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=> d his

     (FILE 'HOME' ENTERED AT 15:58:37 ON 27 NOV 2001)

     FILE 'HCAPLUS' ENTERED AT 15:59:53 ON 27 NOV 2001
L1             8 S AANDAHL E?/AU
L2            61 S  AUKRUST P?/AU
L3            49 S SKALHEGG B?/AU
L4           872 S MULLER F?/AU
L5            56 S FROLAND S?/AU
L6           334 S HANSSON V?/AU
L7          1277 S L1-6
L8           112 S L7 AND CAMP
L9         30784 S ?THIO?(5A)?SUBSTITUT?
L10            2 S L8 AND PKAI
                 SELECT RN L10 1-2

     FILE 'REGISTRY' ENTERED AT 16:10:23 ON 27 NOV 2001
L11            2 S E1-2

     FILE 'HCAPLUS' ENTERED AT 16:11:16 ON 27 NOV 2001
L12            2 S L10 AND L11

     FILE 'REGISTRY' ENTERED AT 16:19:09 ON 27 NOV 2001
L13            1 S  142008-29-5
                 E  CAMP-DEPENDENT PROTEIN KINASE/CN
L14            8 S E30-38
L15            0 S "PKAI"
L16            3 S ?PKAI?/CNS
L17            1 S  60-92-4
                 STR  60-92-4
L18           44 S L18
L19           11 S L19 AND S/ELS
L20          828 S L18 FUL
                 SAVE SCH458P/A L21
L21          226 S L21 AND S/ELS
L22           51 S L22 AND ?PHOSPHOROTHIOATE?/CNS
L23           17 S L23 AND X/ELS
L24           11 S L24 AND S=1
L25            6 S L24 NOT L25

     FILE 'HCAPLUS' ENTERED AT 16:31:34 ON 27 NOV 2001
L26           24 S L25

     FILE 'REGISTRY' ENTERED AT 16:32:07 ON 27 NOV 2001
                 SET SMARTSELECT ON
L27           SEL L13 1- CHEM :       8 TERMS
                 SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 16:32:07 ON 27 NOV 2001
L28        15946 S L28
L29           85 S PKAI OR (PROTEIN KINASE)(3A)TYPE(W)I.ALPHA.
L30          461 S RI.ALPHA.
L31        16218 S L29-31
L32           15 S L27 AND L32
L33           15 S L33 NOT L12
L34            9 S L27 NOT L34
L35        68090 S AIDS OR HIV OR CVI
L36            0 S L36 AND L35
L37          173 S L23
L38          149 S L38 NOT L34-35
L39           63 S L39 AND L32
L40            0 S L39 AND L36
L41
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- inventor search

92 citations with 2 compounds disclosed

828 monophosphothioate cpds

have ~~antig~~ & sulfur

17 are halogenated

11 have 1 sulfur

cAMPS analogs without a halogen

24 citations for L25 cpds

PKAI synonyms

15 cites for PKA & L25 cpds (have a halogen & cAMPS)

L42	10	S L40 AND "TYPE I"
L43	6	S L40 AND EQUATORIAL?
L44	14	S L42-43
L45	0	S L44 AND ?IMMUNO?
L46	15	S L23/THU

14 cites for cAMPS cpds (no halogen) & PKAI

15 cites for any cAMPS analog used for a therapeutic purpose

STR for camps analog

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=> d que l27
L18                 STR
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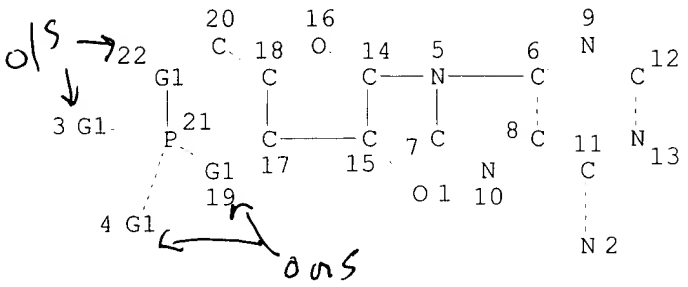


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NODE ATTRIBUTES:
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L21          828 SEA FILE=REGISTRY SSS FUL L18
L22          226 SEA FILE=REGISTRY ABB=ON  PLU=ON  L21 AND S/ELS
L23           51 SEA FILE=REGISTRY ABB=ON  PLU=ON  L22 AND ?PHOSPHOROTHIOATE?/CN
                 S
L24           17 SEA FILE=REGISTRY ABB=ON  PLU=ON  L23 AND X/ELS
L25           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L24 AND S=1
L27           24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25
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=> d ibib abs hitstr 8

L34 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:787966 HCAPLUS
DOCUMENT NUMBER: 123:282000
TITLE: Novel (Rp)-cAMPS analogs as tools for inhibition of cAMP-kinase in cell culture. Basal cAMP-kinase activity modulates interleukin-1.beta. action
AUTHOR(S): Gjertsen, Bjoern T.; Mellgren, Gunnar; Otten, Anne; Maronde, Erik; Genieser, Hans-G.; Jastorff, Bernd; Vintermyr, Olav K.; McKnight, G. Stanley; Doeskeland, Stein O.
CORPORATE SOURCE: Dep. Anat. Cell Biol., Univ. Bergen, Bergen, N-5009, Norway
SOURCE: J. Biol. Chem. (1995), 270(35), 20599-607
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Novel (Rp)-cAMPS analogs differed widely in ability to antagonize cAMP activation of pure **cAMP-dependent protein kinase** I and II and to antagonize actions of cAMP on gene expression, shape change, apoptosis, DNA replication, and protein phosphorylation in intact cells. These differences were related to different abilities of the analogs to stabilize the holoenzyme form relative to the dissocd. form of cAMP kinase type I and II. (Rp)-8-Br-cAMPS and (Rp)-8-Cl-cAMPS were the most potent cAMP antagonists for isolated type I kinase and for cells expressing mostly type I kinase, like IPC-81 leukemia cells, fibroblasts transfected with type I regulatory subunit (RI), and primary hepatocytes. It is proposed that (Rp)-8-Br-cAMPS or (Rp)-8-Cl-cAMPS should replace (Rp)-cAMPS as the first line cAMP antagonist, particularly for studies in cells expressing predominantly type I kinase. The phosphorylation of endogenous hepatocyte proteins was affected oppositely by (Rp)-8-Br-cAMPS and increased cAMP, indicating that (Rp)-8-Br-cAMPS inhibited basal cAMP-kinase activity. The inhibition of basal kinase activity was accompanied by enhanced DNA replication, an effect which could be reproduced by microinjected mutant cAMP-subresponsive RI. It is concluded that the basal cAMP-kinase activity exerts a tonic inhibition of hepatocyte replication. (Rp)-8-Br-cAMPS and microinjected RI also desensitized hepatocytes toward inhibition of DNA synthesis by interleukin-1.beta.. This indicates that basal cAMP-kinase activity can have a permissive role for the action of another (interleukin-1.beta.) signaling pathway.

IT **129735-00-8 142754-27-6**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
((Rp)-cAMPS analogs for inhibition of **protein kinase A** in cell culture)

RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

=> d ibib abs hitstr 1

L12 ANSWER 1 OF 2 HCAPLUS© COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:312118 HCAPLUS
DOCUMENT NUMBER: 132:329307
TITLE: **PKAI** as a potential target for therapeutic intervention
AUTHOR(S): Tasken, K.; **Hansson, V.**; **Aukrust, P.**; **Froland, S.**; **Skalhegg, B. S.**; **Muller, F.**; Tobin, D.; Vang, T.; Torgersen, K. M.; **Aandahl, E. M.**
CORPORATE SOURCE: Institute of Medical Biochemistry, University of Oslo, Oslo, N-0317, Norway
SOURCE: Drug News Perspect. (2000), 13(1), 12-18
CODEN: DNPEED; ISSN: 0214-0934
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 52 refs. We have mapped a mol. mechanism for the impaired T-cell function in HIV infection and common variable immunodeficiency (CVI). Protein kinase A type I (**PKAI**) has a key role as an inhibitor of immune function in T lymphocytes and is activated following antigen receptor triggering. T cells from patients with HIV infection and CVI have increased activation of **PKAI**. This inhibits immune function and proliferation of T cells. Selective antagonists that block **cAMP** action through **PKAI** improve the immune function of T cells from HIV-infected patients up to 300%. Furthermore, combination of **cAMP** antagonists with interleukin-2 normalized immune responses of T cells from all patients examd. and stimulated immune function of T cells from HIV-infected patients up to 600%. In addn., in vitro expts. indicate that approx. 50% of patients with CVI have a T-cell dysfunction that might benefit from a treatment reversing **PKAI** hyperactivation. This outlines **PKAI** as a potentially attractive drug target for immunomodulating therapy in HIV infection, as well as for the treatment of other immunodeficiency disorders such as CVI.
IT **142008-29-5**, Protein kinase A
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**PKAI** as a potential target for therapeutic intervention of immunodeficiency disorders)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 52
REFERENCE(S):
(1) Aandahl, E; AIDS 1999, V13, PF109 HCAPLUS
(2) Aandahl, E; FASEB J 1998, V12, P855 HCAPLUS
(3) Anastassiou, E; J Immunol 1992, V148, P2845 HCAPLUS
(4) Aukrust, P; J Immunol 1999, V162, P1178 HCAPLUS
(7) Chouaib, S; J Immunol 1985, V135, P1172 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind

L12 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2001 ACS
CC 1-0 (Pharmacology)
ST review **PKAI** HIV1 therapy target immunodeficiency; protein kinase AI immunodeficiency target review
IT Human immunodeficiency virus 1
(**PKAI** as a potential target for therapeutic intervention of immunodeficiency disorders)
IT Immunoglobulins
(acquired hypogammaglobulinemia; **PKAI** as a potential target for therapeutic intervention of immunodeficiency disorders)
IT **142008-29-5**, Protein kinase A
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**PKAI** as a potential target for therapeutic intervention of immunodeficiency disorders)

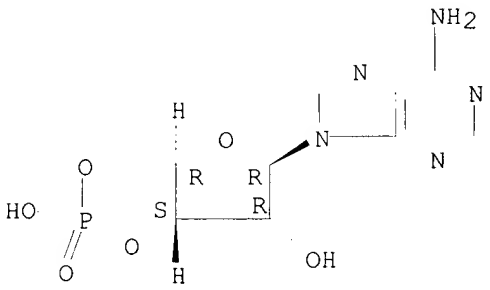
=> d ibib abs hitstr 2

L12 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:90638 HCAPLUS
DOCUMENT NUMBER: 130:251109
TITLE: Increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency
AUTHOR(S): **Aukrust, Pal; Aandahl, Einar Martin ; Skalhegg, Bjorn S.**; Nordoy, Ingvild; **Hansson, Vidar**; Tasken, Kjetil; **Froland, Stig S.**; **Muller, Fredrik**
CORPORATE SOURCE: Medical Department A, Section of Clinical Immunology and Infectious Diseases and Research Institute for Internal Medicine, Rikshospitalet, Oslo, N-0027, Norway
SOURCE: J. Immunol. (1999), 162(2), 1178-1185
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mol. mechanisms underlying the T cell dysfunction often present in common variable immunodeficiency (CVI) are not established. **CAMP** -dependent protein kinase A type I (**PKAI**) is an important inhibitor of T cell proliferation after Ag stimulation. We therefore investigated the possibility that activation of **PKAI** may be involved in the development of T cell dysfunction in CVI. An exogenously added **PKAI**-selective antagonist (Rp-8-Br-**cAMPS**) induced a significant increase in anti-CD3-stimulated PBMC proliferation in 20 CVI patients compared with no effect in 15 controls. Purified T cells from 7 CVI patients with strictly defined T cell deficiency had elevated endogenous **cAMP** levels compared with controls. Treatment of T cells from these CVI patients with Rp-8-bromo-**cAMP** -phosphorothioate markedly improved anti-CD3-stimulated proliferation (up to 3.7-fold), particularly in CD4+ lymphocytes, reaching proliferation levels comparable to control values. No effect of **cAMP** antagonist on T cell proliferation was seen in controls. In these CVI patients, **cAMP** antagonist also increased IL-2 prodn. in anti-CD3-stimulated T cells. However, exogenously added IL-2 at concns. comparable to the achieved increase in IL-2 levels after addn. of **cAMP** antagonist had no effect on T cell proliferation. Furthermore, the stimulatory effects of exogenously added IL-2 at higher concns. and **cAMP** antagonist on T cell proliferation were additive. Our findings indicate that increased **PKAI** activation may be an important mol. basis for the T cell defect in CVI and suggest that the **cAMP**/**PKAI** system may be a potential mol. target for immunomodulating therapy in these patients.
IT **142008-29-5**, **CAMP**-dependent Protein kinase A
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **60-92-4**, **CAMP**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency in relation to)
RN 60-92-4 HCAPLUS

CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 44

REFERENCE(S):

(1) Aandahl, E; FASEB J 1998, V12, P855 HCAPLUS
(3) Anastassiou, E; J Immunol 1992, V148, P2845 HCAPLUS
(5) Aukrust, P; Blood 1995, V86, P1383 HCAPLUS
(6) Aukrust, P; Blood 1996, V87, P674 HCAPLUS
(7) Aukrust, P; Clin Exp Immunol 1992, V89, P211 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 2

L12 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2001 ACS
CC 15-8 (Immunochemistry)
ST protein kinase A T lymphocyte deficiency common variable immunodeficiency
IT Acquired hypogammaglobulinemia
CD4-positive T cell
T cell (lymphocyte)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency)
IT Interleukin 2
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency in relation to)
IT **142008-29-5, CAMP**-dependent Protein kinase A
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency)
IT **60-92-4, CAMP**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency in relation to)

=> d ibib abs hitstr 1

L34 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:645638 HCAPLUS
DOCUMENT NUMBER: 135:208796
TITLE: Induction of development of dopaminergic cells from neural precursors by increasing level of expression of the Nurr1 gene
INVENTOR(S): Bowen, David C.; Johe, Karl K.
PATENT ASSIGNEE(S): NeuralStem Biopharmaceuticals, Ltd., USA
SOURCE: U.S., 38 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

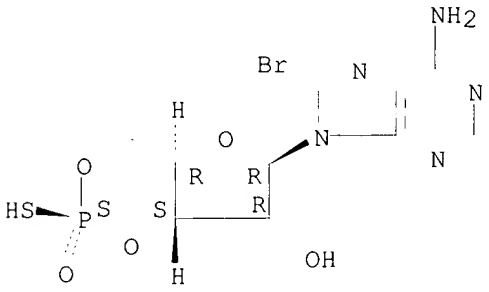
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6284539	B1	20010904	US 1998-169309	19981009

AB The present invention describes a novel method to direct a particular set of fate choice decisions by multipotential precursor cells from the central nervous system. Specifically we show that introducing the gene coding for the nuclear receptor, Nurr1, into central nervous system (CNS) stem cells causes cells to adopt a dopaminergic cell fate. One use of this technol. would be to prep. in vitro neural populations enriched in dopaminergic cells for transplantation in Parkinson's Disease or other neurol. disorders. Furthermore, the finding that Nurr1 expression induces a dopaminergic phenotype suggests that introducing this gene into the brains of patients in which dopaminergic cells are degenerating or have been injured may promote the functional recovery of these neurons and thus the clin. recovery of the patient. Finally, the technol. described in this application could be incorporated into a program of drug screening or gene discovery.

IT **142008-29-5, Protein kinase A**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antagonists of, in induction of dopaminergic neuron differentiation; induction of development of dopaminergic cells from neural precursors by increasing level of expression of Nurr1 gene)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **127634-20-2**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as inhibitor of **protein kinase A** in induction of dopaminergic neuron differentiation; induction of development of dopaminergic cells from neural precursors by increasing level of expression of Nurr1 gene)
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27
REFERENCE(S):
(1) Anon; WO 9404675 1994 HCAPLUS
(2) Carpenter; Exp Neurol 1997, V148, P187 HCAPLUS
(3) Castillo; Genomics 1997, V41, P250 HCAPLUS
(4) Castillo; Mol Cell Neurosci 1998, V11, P36 HCAPLUS
(7) Honkaniemi; Mol Brian Res 1995, V28, P157 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L34 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:161140 HCAPLUS
DOCUMENT NUMBER: 132:203156
TITLE: Cyclic nucleotide-dependent protein kinase activators for promoters of neural regeneration
INVENTOR(S): Song, Hongjun; Poo, Mu-ming; Ming, Guo-li; Tessier-Lavigne, Marc; He, Zhigang
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012099	A1	20000309	WO 1999-US20139	19990902
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6268352	B1	20010731	US 1998-145820	19980902
AU 9957033	A1	20000321	AU 1999-57033	19990902
EP 1109561	A1	20010627	EP 1999-944061	19990902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-145820 A 19980902
WO 1999-US20139 W 19990902

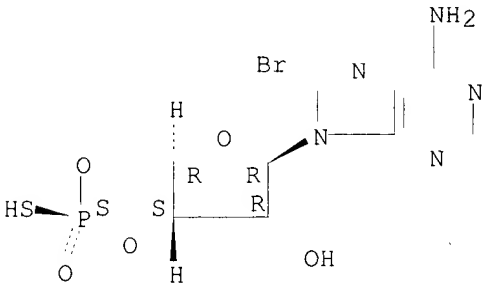
AB Methods and compns. are provided for promoting neural cell growth and/or regeneration. The general methods involve contacting with an activator of a cyclic nucleotide-dependent **protein kinase a** neural cell subject to growth repulsion mediated by a neural cell growth repulsion factor. The activator may comprise a direct or an indirect activator of the protein kinase; the repulsion factor typically comprises one or more natural, endogenous proteins mediating localized repulsion or inhibition of neural cell growth; and the target cells are generally vertebrate neurons, typically injured mammalian neurons. The subject compns. include mixts. comprising a neural cell, an activator of a cyclic nucleotide-dependent protein kinase, and a neural cell growth repulsion factor.

IT **142008-29-5, Protein kinase A**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activators; cyclic nucleotide-dependent protein kinase activators for promoters of neural regeneration)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **127634-20-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic nucleotide-dependent protein kinase activators for promoters of neural regeneration)

RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2
REFERENCE(S):
(1) Genain, C; Proceedings of the National Academy of Sciences of the United States of America 1995, V92, P3601 HCAPLUS
(2) Rydel, R; Proceedings of the National Academy of Sciences of the United States of America 1988, V85, P1257 HCAPLUS

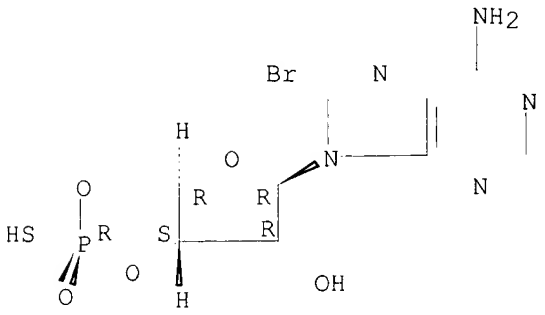
=> d ibib abs hitstr 3

L34 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:22669 HCAPLUS
DOCUMENT NUMBER: 132:333178
TITLE: Additive effects of IL-2 and **protein kinase A** type I antagonist on function of T cells from HIV-infected patients on HAART
AUTHOR(S): Aandahl, Einar Martin; Aukrust, Pal; Muller, Fredrik; Hansson, Vidar; Tasken, Kjetil; Froland, Stig S.
CORPORATE SOURCE: Institute of Medical Biochemistry, University of Oslo, Oslo, N-0317, Norway
SOURCE: AIDS (London) (1999), 13(17), F109-F114
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to explore the basis for a possible immunomodulatory combination therapy with IL-2 and agents inhibiting **protein kinase A** (PKA) type I. Highly active antiretroviral therapy (HAART) has dramatically improved HIV therapy, but fails to eradicate the virus, and the persistence of HIV-assocd. immunodeficiency demonstrates the need for addnl. immunomodulating therapies. The authors have previously shown that hyperactivation of PKA type I inhibits the function of HIV-infected patient T cells. The sep. and combined effect of a PKA type I-selective antagonist (Rp-8-Br-cAMPS) and interleukin (IL)-2 on the function of T cells from HIV-infected patients on HAART was examd. The effect of Rp-8-Br-cAMPS on anti-CD3 stimulated proliferation and IL-2 prodn. and the combined effect with exogenous IL-2 were studied in vitro with cells from 13 HIV-infected patients on HAART and 6 uninfected controls. The PKA type I-selective antagonist improved cell proliferation (median 1.5-fold, maximal 2.8-fold) and IL-2 prodn. (median 1.5-fold, maximal 2.4-fold) in T cells from HIV-infected patients on HAART, but not in controls. The addn. of IL-2 enhanced proliferation of T cells from HIV-infected patients (approx. 1.9-fold) and that of controls (approx. 1.4-fold), but IL-2 had no effect at the concns. produced by treatment with PKA type I antagonist. However, the combined effect of IL-2 and PKA type I antagonist was additive and resulted in a further increase in T-cell proliferation (median 2.5-fold, maximal 5.8-fold), reaching levels comparable with those of uninfected controls in most of the patients. The authors' findings thus suggest a basis for a novel strategy in treatment of HIV infection by combining IL-2 therapy and treatment modalities counteracting PKA type I activity with HAART.

IT **129735-00-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additive effects of interleukin-2 and **protein kinase A** type I antagonist on function of T cells from HIV-infected patients on HAART)
RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5, Protein kinase A**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type I, antagonist; additive effects of interleukin-2 and **protein kinase A** type I antagonist on function of T cells from HIV-infected patients on HAART)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 25
REFERENCE(S):
(1) Aandahl, E; FASEB J 1998, V12, P855 HCAPLUS
(2) Anastassiou, E; J Immunol 1992, V148, P2845 HCAPLUS
(3) Aukrust, P; Clin Exp Immunol 1992, V89, P211 HCAPLUS
(6) Chouaib, S; J Immunol 1985, V135, P1172 HCAPLUS
(7) Chun, T; Nature Med 1999, V5, P651 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 4

L34 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:69194 HCAPLUS
DOCUMENT NUMBER: 130:277074
TITLE: **Protein kinase A** inhibition and PACAP-induced insulin secretion in HIT-T15 cells
AUTHOR(S): Filipsson, Karin; Ahren, Bo
CORPORATE SOURCE: Department of Medicine, Malmo University Hospital, Lund University, Malmo, SE-205 02, Swed.
SOURCE: Ann. N. Y. Acad. Sci. (1998), 865(VIP, PACAP, and Related Peptides), 441-444
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The importance of the increase in cellular cAMP content for the stimulation of exocytosis by pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) may be studied by inhibiting **protein kinase A** (PKA) as PKA is activated by cAMP and thought to mediate its actions. For this purpose it is necessary to use a reliable PKA inhibitor. In this study the authors have examd. the effects of three PKA inhibitors: Rp-cAMPS, Rp-8-Br-cAMPS and H89 (N-[2-(p-bromocinnamylamino)ethyl]-5-isoquinoline sulfonamide) on PACAP38 and forskolin-stimulated insulin secretion in HIT-T15 cells. In the first series of expts., the authors verified previous results that after 60-min incubation, PACAP38 or forskolin at 10 mM glucose potentiates insulin secretion. When incubating the cells for 60 min in the presence of either of the three PKA inhibitors, the authors found that none of them inhibited insulin secretion after stimulation with PACAP38, and that only Rp-8-Br-cAMPS could slightly inhibit the response to forskolin. The effect of glucose on insulin secretion was not affected by any of the three PKA inhibitors. The failure of the PKA inhibitors to inhibit insulin secretion might be explained by a too long (60 min) incubation time. Therefore the authors shortened the incubation time to 15 min. The authors then found that Rp-cAMPS and Rp-8-Br-cAMPS still had no effect on glucose, PACAP38-, or forskolin-induced insulin secretion. However H89 decreased insulin levels at 10 mM glucose from 1170 pmol/l in controls to 1010 pmol/l, and PACAP38-induced insulin secretion was inhibited from 2230 pmol/l in controls to 1410 pmol/l. Similarly, the forskolin-induced insulin secretion was inhibited from 2690 pmol/l in the absence of H89 to 1920 pmol/l with the inhibitor. In conclusion both the PACAP38- and the forskolin-induced insulin secretion were inhibited by approx. 35% by H89 after 15-min incubation, whereas the Rp-isomers of cAMP were ineffective. The PKA inhibitor most suitable for the authors' cell system is H89 and the inhibition of PKA is best studied during shorter time periods. With H89, therefore, the contribution of cAMP for PACAP-induced insulin secretion in HIT-T15 cells might be examd. in further studies.

IT **142008-29-5, Protein kinase A**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**protein kinase A** inhibition in relation to contribution of cAMP for PACAP-induced insulin secretion in HIT-T15 cells)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

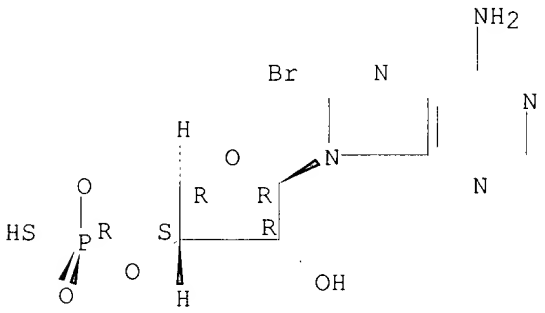
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **129735-00-8**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(**protein kinase A** inhibition in relation
to contribution of cAMP for PACAP-induced insulin secretion in HIT-T15
cells)

RN 129735-00-8 HCAPLUS

CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S):

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(4) Fridolf, T; Cell Tissue Res 1992, V269, P275 HCAPLUS
(5) Hidaka, H; Essays Biochem 1994, V28, P73 HCAPLUS
(6) Holz, G; J Biol Chem 1995, V270, P17749 HCAPLUS
(7) Straub, S; J Biol Chem 1996, V271, P1660 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 5

L34 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:719272 HCAPLUS
DOCUMENT NUMBER: 130:490
TITLE: Use of compounds inhibiting **cAMP-dependent protein kinase A** as immunomodulating agents for treating immunosuppressive diseases
INVENTOR(S): Tasken, Kjetil; Aandahl, Einar Martin; Aukrust, Pal; Skalhegg, Bjorn S.; Muller, Fredrik; Froland, Stig; Hansson, Vidar
PATENT ASSIGNEE(S): Norway
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9848809	A1	19981105	WO 1998-NO134	19980429
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9870865	A1	19981124	AU 1998-70865	19980429
EP 1024809	A1	20000809	EP 1998-917808	19980429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 9905269	A	19991213	NO 1999-5269	19991028

PRIORITY APPLN. INFO.: NO 1997-1997 A 19970429
WO 1998-NO134 W 19980429

AB Several compds. capable of inhibiting **cAMP-dependent protein kinase A** (PKA) are used to produce a medicament increasing T-cell proliferation in patients with immunosuppressive diseases. Inhibitors include cAMP analogs, ribozymes, antisense DNA, and peptides binding to the anchoring region of PKA. In T-cells from normal blood donors, TCR/CD3-stimulated T-cell proliferation was inhibited by a cAMP agonist (Sp-8-Br-cAMPS). This effect was almost completely reversed by increasing concns. of complementary antagonist (Rp-8-Br-cAMPS (I)). However, antagonist alone did not alter proliferation of normal T-cells. In contrast, when the TCR/CD3-induced proliferation of T-cells from a HIV-infected patient was investigated, I not only reversed the effect of the complementary agonist, but further increased the proliferation above the levels in untreated cells. When the effect of the antagonist alone was assessed in T-cells from HIV-infected patients, there was a concn.-dependent increase in TCR/CD3-induced proliferation that was more than 2-fold at higher concns. T-cells responding poorly to TCR/CD3 stimulation benefitted most from cAMP antagonist treatment.

IT **142008-29-5, cAMP-dependent protein kinase A**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(Type I; **cAMP-dependent protein**

kinase A inhibitors as immunomodulating agents for treating immunosuppressive diseases)

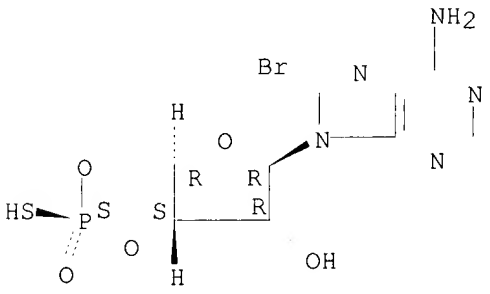
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **127634-20-2**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(as cAMP agonist, TCR/CD3-stimulated proliferation of T-cells inhibition by; **cAMP-dependent protein kinase A** inhibitors as immunomodulating agents for treating immunosuppressive diseases)

RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

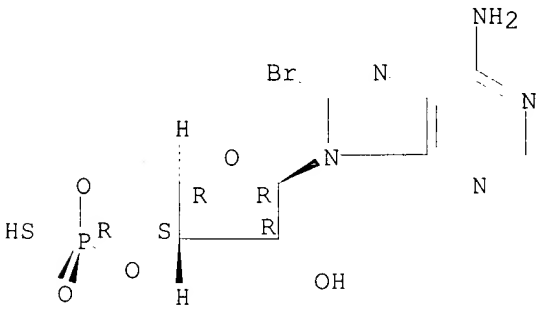
Absolute stereochemistry.



IT **129735-00-8 142754-27-6 215597-30-1**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(as cAMP antagonist; **cAMP-dependent protein kinase A** inhibitors as immunomodulating agents for treating immunosuppressive diseases)

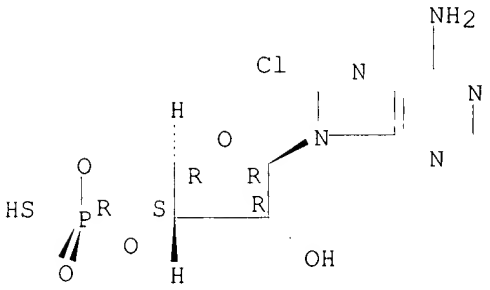
RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



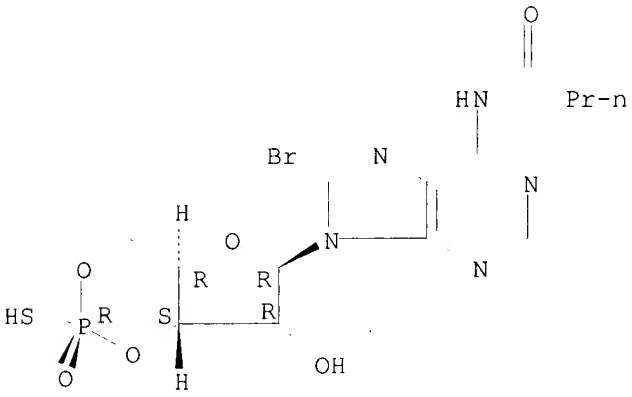
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 215597-30-1 HCAPLUS
CN Adenosine, 8-bromo-N-(1-oxobutyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



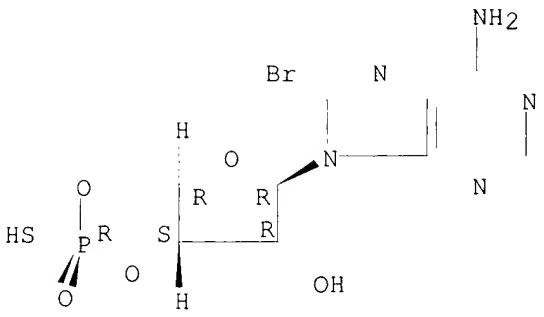
REFERENCE COUNT: 5
REFERENCE(S):
(1) Hybridon Inc; WO 9711171 A1 1997 HCAPLUS
(2) Icos Corporation; WO 9704096 A1 1997 HCAPLUS
(3) The Regents Of The University Of California; WO 9319766 A1 1993 HCAPLUS
(4) The Secretary Department Of Health And Human Services; WO 9321929 A1 1993 HCAPLUS
(5) University Research Corporation; WO 9416736 A1 1994 HCAPLUS

=> d ibib abs hitstr 6

L34 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:434799 HCAPLUS
DOCUMENT NUMBER: 129:170140
TITLE: **Protein kinase A** type I antagonist restores immune responses of T cells from HIV-infected patients
AUTHOR(S): Aandahl, Einar Martin; Aukrust, Pal; Skalhegg, Bjorn S.; Muller, Fredrik; Froland, Stig S.; Hansson, Vidar; Tasken, Kjetil
CORPORATE SOURCE: Institute of Medical Biochemistry, University of Oslo, Oslo, N-0317, Norway
SOURCE: FASEB J. (1998), 12(10), 855-862
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **CAMP-dependent protein kinase A** (PKA) type I has been established as an acute inhibitor of T cell activation. For this reason, we investigated the possible role of PKA type I in HIV-induced T cell dysfunction. T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analog than are normal T cells. A PKA type I-selective antagonist increases the impaired proliferation of T cells from HIV-infected patients to normal or subnormal levels (up to 2.8-fold). Follow-up of patients after initiation of highly active antiretroviral treatment revealed that a majority of patients have a persistent T cell dysfunction that is normalized by incubation of T cells with Rp-8-Br-cAMPS. These observations imply that increased activation of PKA type I may contribute to the progressive T cell dysfunction in HIV infection and that PKA type I may be a potential target for immunomodulating therapy.
IT **142008-29-5, Protein kinase A**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**protein kinase A** type I antagonist restores immune responses of T cells from HIV-infected patients)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **129735-00-8**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**protein kinase A** type I antagonist restores immune responses of T cells from HIV-infected patients)
RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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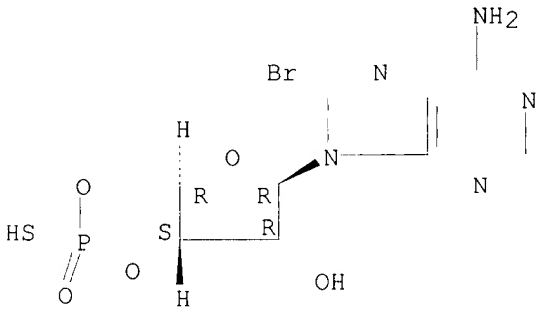
L34 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:101257 HCAPLUS
DOCUMENT NUMBER: 126:315491
TITLE: Hypoxic inhibitor of K+ currents in isolated rat type I carotid body cells. Evidence against the involvement of cyclic nucleotides
AUTHOR(S): Hatton, C. J.; Peers, C.
CORPORATE SOURCE: Institute Cardiovascular Research, Leeds University, Leeds, LS2 9JT, UK
SOURCE: Pfluegers Arch. (1996), 433(1-2), 129-135
CODEN: PFLABK; ISSN: 0031-6768
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Whole-cell patch-clamp recordings were used to evaluate the effects of cAMP and cGMP on ionic currents in type I carotid body cells isolated from rat pups, and to investigate whether cyclic nucleotides are involved in K+ current inhibition by hypoxia. In the presence of 500 .mu.M isobutylmethylxanthine, currents were not modified by 8-bromo-cAMP (2 mM), dibutyryl-cAMP (5 mM), or 8-bromo-cGMP (2 mM). Currents were also unaffected by the phosphodiesterase (PDE)-resistant **protein kinase A** activators Sp-cyclic adenosine-3',5'-monophosphorothioate (Sp-cAMPS) and Sp-8-bromoadenos-ine-3',5'-monophosphorothioate (Sp-8-bromo-cAMPS) (50 .mu.M), or by .beta.-phenyl-1,N2-ethenoguanosine-3',5'-cyclic monophosphate (PET-cGMP) (100 .mu.M), or the nitric oxide donor S-nitroso-N-acetylpenicillamine (SNAP; 500 .mu.M). Ca2+ channel currents were also unaffected by Sp-8-Br-cAMPS, PET-cGMP and SNAP at the same concns. In the absence of cyclic nucleotide analogs, hypoxia (PO2 17-23 mmHg) reversibly inhibited K+ currents. This degree of hypoxic inhibition was not altered by the PDE-resistant **protein kinase A** inhibitors Rp-cyclic adenosine-3',5'-monophosphoro-thioate (Rp-cAMPS) (50 .mu.M) or Rp-8-bromoadenosine-3',5'-monophosphorothioate (Rp-8-bromo-cAMPS) (200 .mu.M). Similarly, PET-cGMP (100 .mu.M) and SNAP (500 .mu.M) did not alter the degree of inhibition caused by hypoxia. At the same concns. used in type I cell expts., Sp-8-bromo-cAMPS, PET-cGMP and SNAP completely relaxed isolated guinea-pig basilar arteries preconstricted with 20 mM K+-contg. solns. Our results indicate that cyclic nucleotides alone are not an important factor in the regulation by O2 tension of K+ currents in rat type I carotid body cells.

IT **152322-58-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cyclic nucleotides without effects on regulation by O2 tension of K+ currents in isolated rat type I carotid body cells)

RN 152322-58-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.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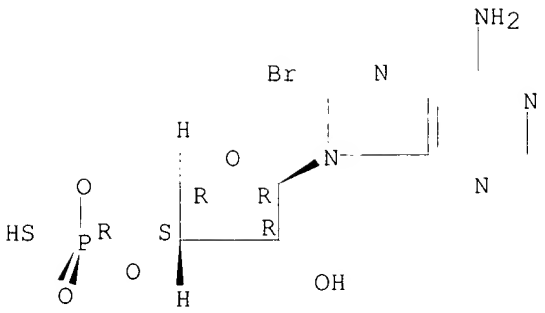
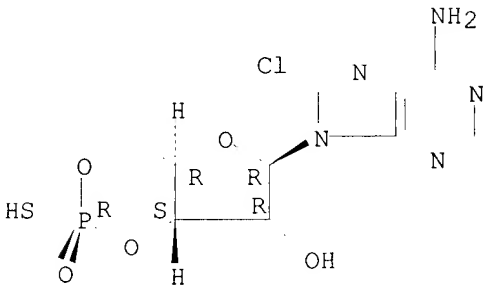


RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5, CAMP-dependent protein kinase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(I and II; (Rp)-cAMPS analogs for inhibition of **protein kinase A** in cell culture)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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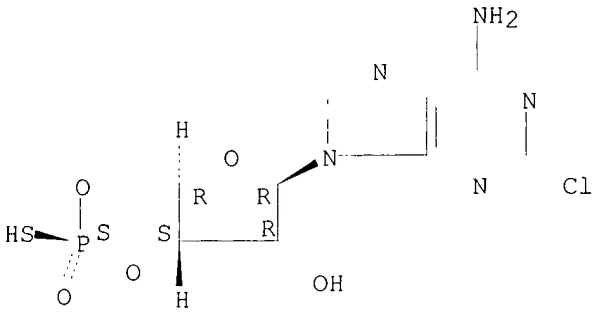
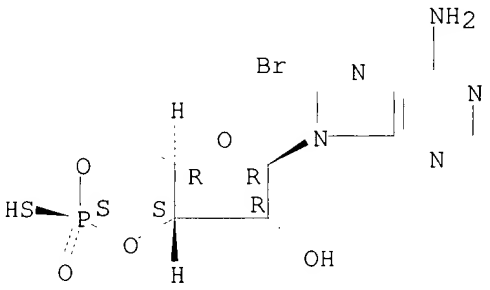
L34 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:656486 HCAPLUS
DOCUMENT NUMBER: 123:131990
TITLE: Evidence for several pathways of biological response to hydrolyzable cAMP-analogs using a model system of apoptosis in IPC-81 leukemia cells
AUTHOR(S): Ruchaud, S.; Zorn, M.; Davilar-Villar, E.; Genieser, H. G.; Hoffmann, C.; Gjersten, B. T.; Doeskeland, S. O.; Jastorff, B.; Lanoote, M.
CORPORATE SOURCE: Centre G. Hayfem, Hopital St-Louis, Paris, Fr.
SOURCE: Cell. Pharmacol. (1995), 2(3), 127-40
CODEN: CEPHEG; ISSN: 1351-3214
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Degradable and undegradable cAMP analogs with a wide range of rationally selected (testkit concept) chem. modifications were studied for their apoptotic potency in the rat IPC-81 model for acute myelocytic leukemia. The biol. activity of corresponding 5'AMP and adenosine metabolites was compared. To discriminate a cA-kinase response from non-kinase effects the authors used a subclone of the IPC-81 line with a sub-responsiveness to cA-kinase I activation by cAMP analogs. As proven by HPLC, only cAMP analogs with an axial (Sp) and equatorial (Rp) substitution at the phosphate moiety were partially or totally resistant against metab. in cell culture. Heat inactivation of serum only reduced but not prevented the formation of metabolites. The results gave different dose responses due to the type of modification at the signal mols. and the type of cell line. Undegradable cAMP analogs only induced apoptosis via the cA-kinase pathway in the two cell lines; most efficiently through the highly lipophilic, resistant and cA-kinase specific analog Sp-DCl-cBIMPS. The lipophilic cAMP antagonist Rp-8Cl-cAMPS inhibited the induction of apoptosis by its corresponding Sp-8Cl-cAMPS in a dose-dependent manner. Degradable cAMP analogs act via the cyclic nucleotides and/or their metabolites. Rationale for the different types of responses based on structure activity relations are discussed and mechanisms of actions are proposed. The authors' study supports an essential participation of the cAMP signaling pathway in induction of apoptosis, if a highly cooperative way of cell death is induced. Exclusively via the cAMP signaling cascade, an analog will act only if the deriv. is undegradable, highly membrane permeable and a potent cA-kinase activator. Degradable analogs exhibit their effects through diverse mechanisms. Detailed biochem. and cell biol. studies with the complete set of catabolites and metabolites of those derivs., which exhibit the highest activity, allow the design of a new generation of nucleosides and nucleotides with high, hopefully cell type selective, potential for apoptosis in tumor cells.
IT **124854-63-3**, Adenosine, 2-chloro-, cyclic 3',5'-(hydrogen phosphorothioate), (S)- **127634-20-2 142754-27-6 142754-28-7**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(evidence for several pathways of biol. response to hydrolyzable cAMP-analogs using a model system of apoptosis in IPC-81 leukemia cells)
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-27-6 HCAPLUS
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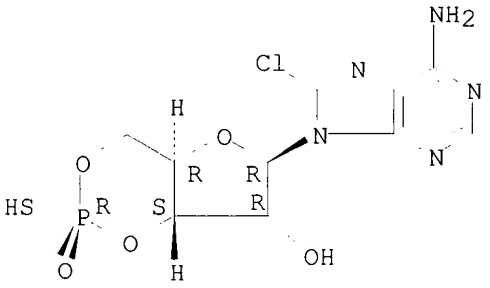
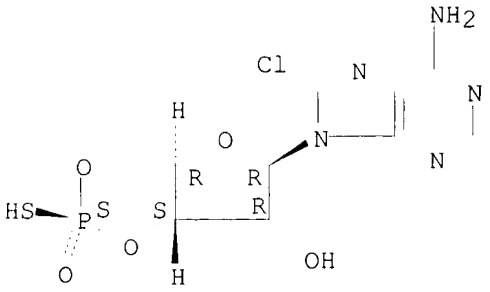
Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(evidence for several pathways of biol. response to hydrolyzable cAMP-analogs using a model system of apoptosis in IPC-81 leukemia cells)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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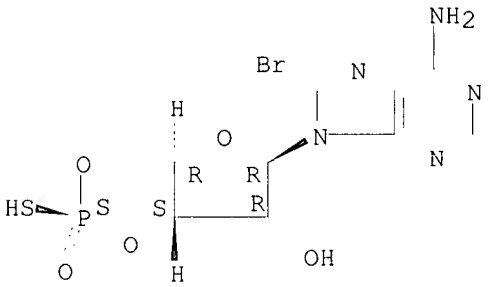
L34 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:640175 HCAPLUS
DOCUMENT NUMBER: 123:108824
TITLE: Regulation of RCK1 currents with a cAMP analog via enhanced protein synthesis and direct channel phosphorylation
AUTHOR(S): Levin, Gal; Keren, Tal; Peretz, Tuvia; Chikvashvili, Dodo; Thornhill, William B.; Lotan, Ilana
CORPORATE SOURCE: Dep. Physiology and Pharmacology, Tel-Aviv Univ., Ramat Aviv, 69978, Israel
SOURCE: J. Biol. Chem. (1995), 270(24), 14611-18
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have recently shown that the rat brain Kv1.1 (RCK1) voltage-gated K+ channel is partially phosphorylated in its basal state in Xenopus oocytes and can be further phosphorylated upon treatment for a short time with a cAMP analog. In this study, we show, by two-electrode voltage clamp anal., that whereas treatments for a short time with various cAMP analogs do not affect the channel function, prolonged treatment with 8-bromoadenosine 3',5'-cyclic monophosphorothioate ((Sp)-8-Br-cAMPS), a membrane-permeant cAMP analog, enhances the current amplitude. It also enhances the current amplitude through a mutant channel that cannot be phosphorylated by **protein kinase A** activation. The enhancement is inhibited in the presence of (Rp)-8-Br-cAMPS, a membrane-permeant **protein kinase A** inhibitor. Concomitant SDS-PAGE anal. reveals that this treatment not only brings about phosphorylation of the wild-type channel, but also increases the amts. of both wild-type and mutant channel proteins; the latter effect can be inhibited by cycloheximide, a protein synthesis inhibitor. In the presence of cycloheximide, the (Sp)-8-Br-cAMPS treatment enhances only the wild-type current amplitudes and induces accumulation of wild-type channels in the plasma membrane of the oocyte. In summary, prolonged treatment with (Sp)-8-Br-cAMPS regulates RCK1 function via two pathways, a pathway leading to enhanced channel synthesis and a pathway involving channel phosphorylation that directs channels to the plasma membrane.

IT **127634-20-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cAMP analog regulation of RCK1 potassium channel dependence on protein synthesis and channel phosphorylation)

RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 11

L34 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:603959 HCAPLUS
DOCUMENT NUMBER: 123:17877
TITLE: Method of inducing vasorelaxation to treat pulmonary hypertension
INVENTOR(S): Lawson, Charles A.; Pinsky, David J.; Smerling, Arthur; Stern, David M.
PATENT ASSIGNEE(S): Trustees of Columbia University in the City of New York, USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

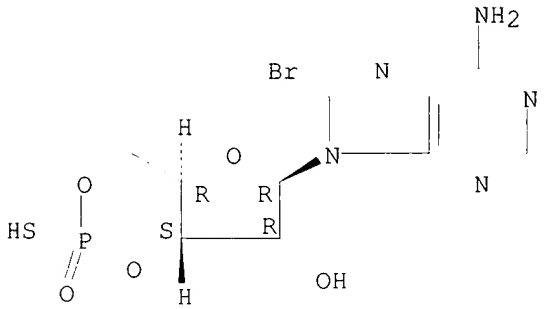
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509636	A1	19950413	WO 1994-US11248	19941004
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5728705	A	19980317	US 1993-131984	19931004
AU 9479652	A1	19950501	AU 1994-79652	19941004
US 5968911	A	19991019	US 1997-362571	19970218

PRIORITY APPLN. INFO.: US 1993-131984 19931004
WO 1994-US11248 19941004

AB A method of selectively decreasing pulmonary vascular resistance in a subject comprises administering endobronchially a drug chosen from cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs, as aerosol solns. or powders.

IT **152322-58-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aerosols contg. vasorelaxants for treatment of pulmonary hypertension)
RN 152322-58-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5D, Protein kinase A,** agonists
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aerosols contg. vasorelaxants for treatment of pulmonary hypertension)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 12

L34 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:69593 HCAPLUS
DOCUMENT NUMBER: 120:69593
TITLE: Phosphorothioate derivatives of cyclic AMP analogs for inhibition of cell proliferation
INVENTOR(S): Jastorff, Bernd; Genieser, Hans Gottfried; Cho-Chung, Yoon Sang
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

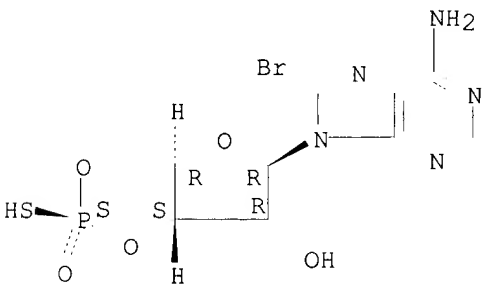
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9321929	A1	19931111	WO 1993-US4093	19930430
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9342266	A1	19931129	AU 1993-42266	19930430
US 5843916	A	19981201	US 1994-225097	19940408
PRIORITY APPLN. INFO.:			US 1992-877523	19920501
			WO 1993-US4093	19930430

AB A method of inhibiting the proliferation of cells, particularly cancerous cells, by contacting the cells with a phosphorothioate deriv. of a cAMP modified at either or both of the C-6 and C-8 positions of the adenine moiety, and pharmaceutical compns. therefor are disclosed. At 50 .mu.M, 8-chloro-, 8-methylthio-, and 8-bromo-cAMP phosphorothioate derivs. exhibited 40-75% growth inhibition of breast and colon cancer cell lines. Effects of combinations of compds. on growth inhibition were also studied.

IT **127634-20-2 142754-27-6 152218-15-0**
152322-57-1 152322-58-2
RL: BIOL (Biological study)
(cell proliferation inhibition with)

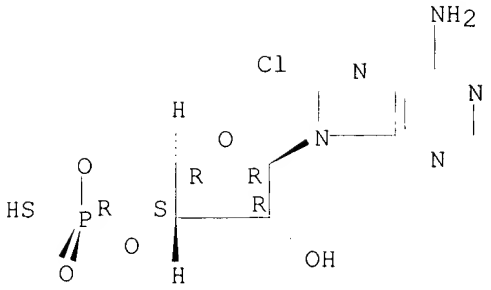
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



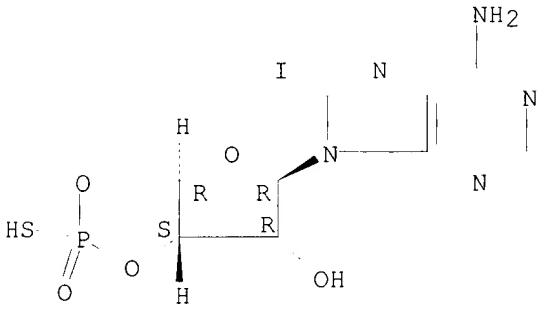
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



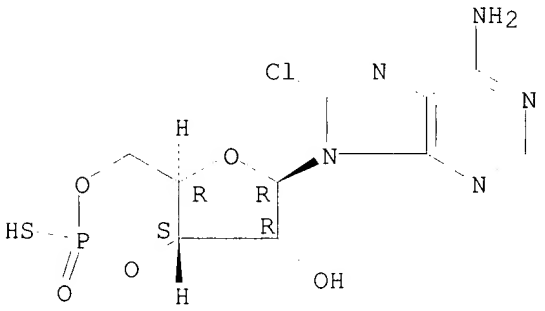
RN 152218-15-0 HCAPLUS
CN Adenosine, 8-iodo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



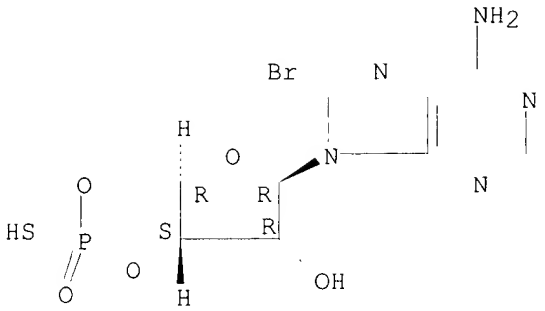
RN 152322-57-1 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



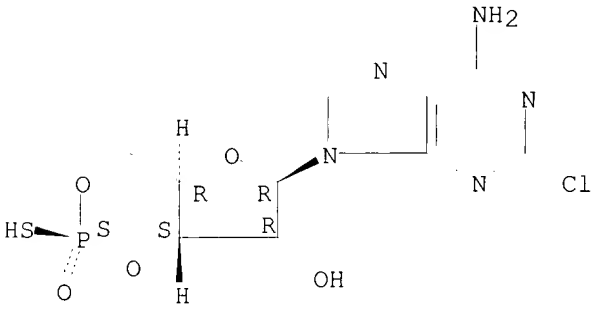
RN 152322-58-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



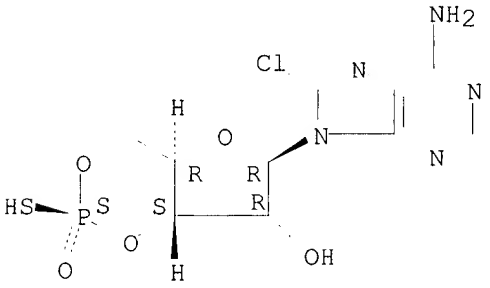
IT **124854-63-3 142754-28-7**
RL: BIOL (Biological study)
(human colon carcinoma cells inhibition with)
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5, CAMP-dependent protein kinase**
RL: BIOL (Biological study)
(phosphorothioate derivs. of cAMP analogs as antagonists of)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

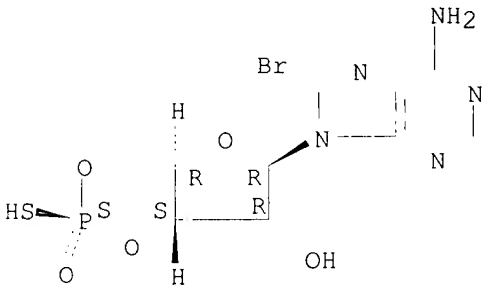
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 13

L34 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:421507 HCAPLUS
DOCUMENT NUMBER: 119:21507
TITLE: Cell-permeable non-hydrolyzable cAMP derivatives as tools for analysis of signaling pathways controlling gene regulation in Dictyostelium
AUTHOR(S): Schaap, Pauline; van Ments-Cohen, Martine; Soede, Ron D. M.; Brandt, Raymond; Firtel, Richard A.; Dostmann, Wolfgang; Genieser, Hans Gottfried; Jastorff, Bernd; van Haastert, Peter J. M.
CORPORATE SOURCE: Dep. Biol., Univ. Leiden, Leiden, 2311 GP, Neth.
SOURCE: J. Biol. Chem. (1993), 268(9), 6323-31
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A novel class of cAMP derivs. were tested for binding to surface cAMP receptors (CAR), **protein kinase A** (PKA), and cAMP-phosphodiesterase (PDE) and for induction of three classes of cAMP regulated genes in Dictyostelium discoideum. These derivs. carry sulfur substitutions for either the axial (Sp) or equatorial (Rp) exocyclic oxygen atoms, while further modifications were introduced to provide specificity for binding to either CAR or PKA, and/or to increase lipophilicity and render the derivs. membrane-permeable. All derivs. bind weakly to PDE and are almost not degraded during incubation with Dictyostelium cells. One cAMP deriv., 6-thioethylpurineriboside 3',5'-monophosphorothioate, Sp-isomer (Sp-6SEtcPuMPS), fulfills the criteria for selective activation of PKA in vivo. The compd. enters Dictyostelium cells and reaches an intracellular concn. of 1 .mu.M, sufficient to active PKA, at an extracellular concn. of 30 .mu.M, which is insufficient to active CAR. Expression of cAMP-regulated prespore and prestalk genes and the aggregative PDE gene are effectively induced by CAR agonists and very poorly by PKA agonists. Even Sp-6SEtcPuMPS is ineffective to induce gene expression. These data not only indicate that surface cAMP receptors are the first targets for cAMP-induced gene expression, but argue against direct induction of expression of these genes by cAMP-induced PKA activation.
IT **142008-29-5, Protein kinase A**
RL: USES (Uses)
(cAMP phosphorothioates binding affinity for, cAMP-induced gene expression in Dictyostelium discoideum in relation to)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

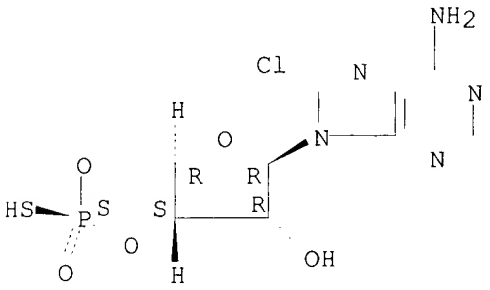
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **127634-20-2 142754-28-7**
RL: USES (Uses)
(cAMP receptor and **protein kinase A** and cAMP-phosphodiesterase binding affinity of and response of Dictyostelium cAMP-regulated genes to)
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

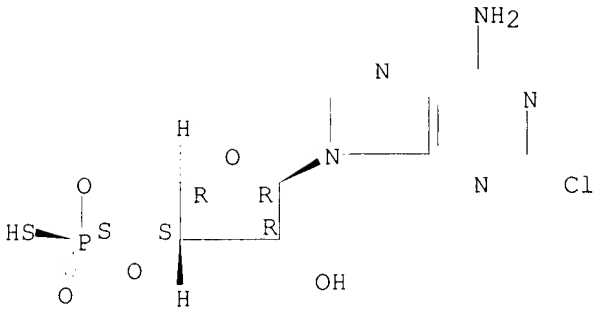


=> d ibib abs hitstr 14

L34 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:503568 HCAPLUS
DOCUMENT NUMBER: 117:103568
TITLE: Unhydrolyzable analogs of adenosine 3':5'-monophosphate demonstrating growth inhibition and differentiation in human cancer cells
AUTHOR(S): Yokozaki, Hiroshi; Tortora, Giampaolo; Pepe, Stefano; Maronde, Erik; Genieser, Hans Gottfried; Jastorff, Bernd; Cho-Chung, Yoon S.
CORPORATE SOURCE: Lab. Tumor Immunol. Biol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cancer Res. (1992), 52(9), 2504-8
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A set of adenosine 3':5'-monophosphate (cAMP) analogs that combine exocyclic sulfur substitutions in the equatorial (Rp) or the axial (Sp) position of the cyclophosphate ring with modifications in the adenine base of cAMP were tested for their effect on the growth of HL-60 human promyelocytic leukemia cells and LS-174T human colon carcinoma cells. Both diastereomers of the phosphorothioate derivs. were growth inhibitory, exhibiting a concn. inhibiting 50% of cell proliferation of 3-100 .mu.M. Among the analogs tested, Rp-8-Cl-cAMPS and Sp-8-Br-cAMPS were the two most potent. Rp-8-Cl-cAMPS was 5- to 10-fold less potent than 8-Cl-cAMP while Sp-8-Br-cAMPS was approx. 6-fold more potent than 8-Br-cAMP. The growth inhibition was not due to a block in a specific phase of the cell cycle or due to cytotoxicity. Rp-8-Cl-cAMPS enhanced its growth-inhibitory effect when added together with 8-Cl-cAMP and increased differentiation in combination with N6-benzyl-cAMP. The binding kinetics data showed that these Sp and Rp modifications brought about a greater decrease in affinity for Site B than for Site A of RI (the regulatory subunit of type I **cAMP-dependent protein kinase**) and a substantial decrease of affinity for Site A or RII (the regulatory subunit of type II protein kinase) but only a small decrease in affinity for Site B of RII, indicating the importance of the Site B binding of RII in the growth-inhibitory effect. These results show that the phosphorothioate analogs of cAMP are useful tools to investigate the mechanism of action of cAMP in growth control and differentiation and may have practical implication in the suppression of malignancy.
IT **142008-29-5**
RL: BIOL (Biological study)
(I and II, RI and RII regulatory subunits of, binding of unhydrolyzable analogs of cAMP to, growth inhibition and differentiation induction activity of, in human cancer cells, structure in relation to)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

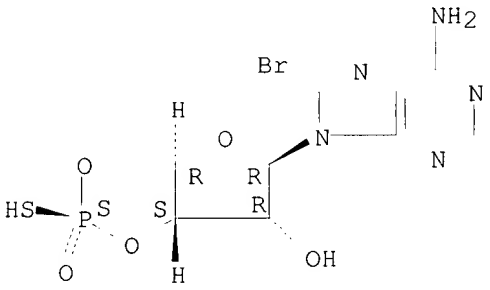
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **124854-63-3 127634-20-2 142754-28-7 143168-14-3**
RL: BIOL (Biological study)
(growth inhibition and differentiation inducing activity of, in human cancer cells, structure in relation to)
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



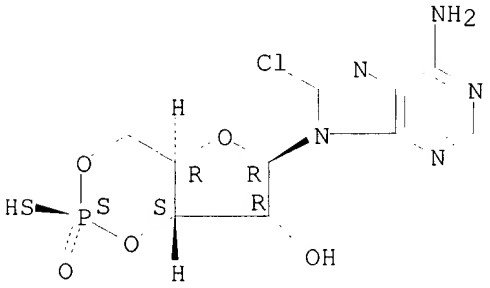
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

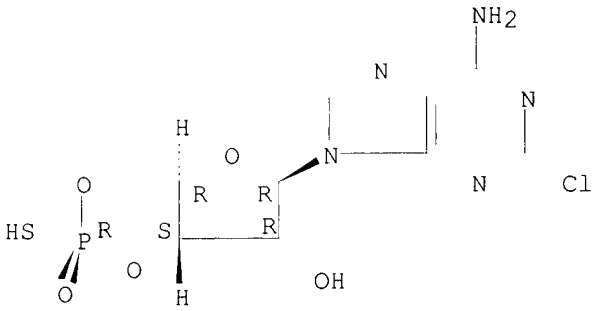


RN 143168-14-3 HCAPLUS

=> d ibib abs hitstr 15

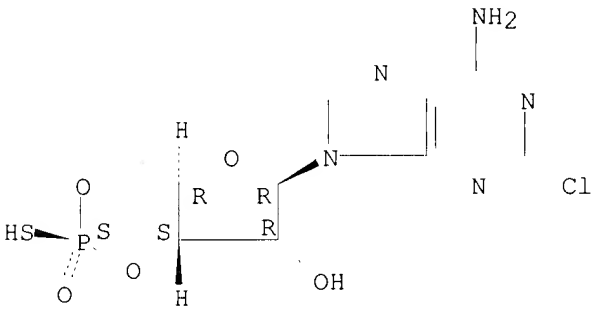
L34 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:547947 HCAPLUS
DOCUMENT NUMBER: 113:147947
TITLE: Probing the cyclic nucleotide binding sites of **cAMP-dependent protein kinases** I and II with analogs of adenosine 3',5'-cyclic phosphorothioates
AUTHOR(S): Dostmann, Wolfgang R. G.; Taylor, Susan S.; Genieser, Hans Gottfried; Jastorff, Bernd; Doeskeland, Stein Ove; Oegreid, Dagfinn
CORPORATE SOURCE: Dep. Chem., Univ. California, San Diego, La Jolla, CA, 92093, USA
SOURCE: J. Biol. Chem. (1990), 265(18), 10484-91
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A set of cAMP analogs were synthesized that combined exocyclic S substitutions in the equatorial (Rp) or the axial (Sp) position of the cyclophosphate ring with modifications in the adenine base of cAMP. The potency of these compds. to inhibit the binding of [3H]cAMP to sites A and B from type I (rabbit skeletal muscle) and type II (bovine myocardium) **cAMP-dependent protein kinase** was detd. quant. On the av., the Sp isomers had a 5-fold lower affinity for site A and a 30-fold lower affinity for site B of isoenzyme I than their cyclophosphate homolog. The mean redn. in affinities for the equiv. sites of isoenzyme II were 20- and 4-fold, resp. The Rp isomers showed a decrease in affinity of .apprx.400- and .apprx.200-fold for sites A and B, resp., of isoenzyme I, against 200- and 45-fold for sites A and B of isoenzyme II. The Sp substitutions therefore increased the relative preference for site A of isoenzyme I and site B of isoenzyme II. The Rp substitutions, on the other hand, increased the relative preference for site B of both isoenzymes. These data showed that the Rp and Sp substitutions are tolerated differently by the 2 intrachain sites of isoenzymes I and II. They also support the hypothesis that it is the axial, and not the previously proposed equatorial O atom that contributes the neg. charge for the ionic interaction with an invariant arginine in all 4 binding sites. In addn., they demonstrate that combined modifications in the adenine ring and the cyclic phosphate ring of cAMP can enhance the ability to discrimin.alpha.te between site A and B of 1 isoenzyme as well as to discriminate between isoenzyme I and II. Since Rp analogs of cAMP are known to inhibit activation of **cAMP-dependent protein kinases**, the findings of the present study have implications for the synthesis of analogs having a very high selectivity for isoenzyme I or II.
IT **124844-92-4 124854-63-3 127634-20-2 129735-00-8**
RL: BIOL (Biological study)
(protein kinases I and II cAMP-dependent binding sites A and B differential binding affinity for)
RN 124844-92-4 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(R)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



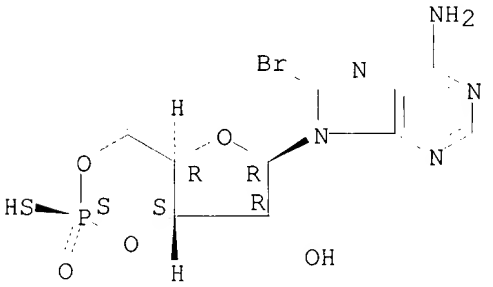
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



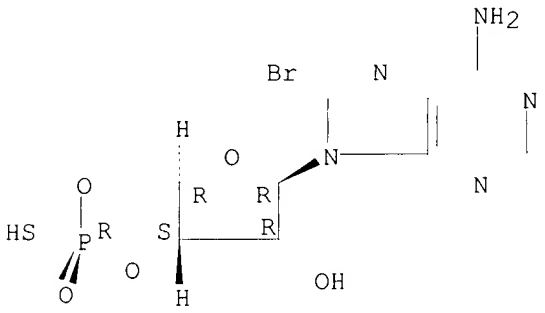
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.


NH2
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O
H
OH

=> d ibib abs hitstr 1

L46 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:93872 HCAPLUS
DOCUMENT NUMBER: 134:157586
TITLE: Use of substances increasing the intracellular content of cyclic AMP or stimulating activity of cyclic AMP binding proteins for the treatment of illnesses of the bladder
INVENTOR(S): Truss, Michael Carsten; Stief, Christian G.; Jonas, Udo; Uckert, Stefan; Becker, Armin J.; Forssmann, Wolf-Georg
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

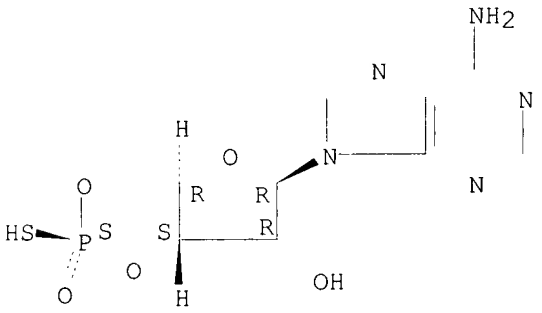
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19935209	A1	20010208	DE 1999-19935209	19990727

AB The invention discloses the use of substances increasing the intracellular concn. of cAMP (cAMP) by direct stimulation of adenyl cyclase activity, assocg. with .beta. receptors, or inhibiting cAMP-hydrolyzing phosphodiesterases 1, 2, 3, 4, 7, or 8, or stimulate the functional activity of cAMP binding proteins, for the treatment of urinary bladder storage function disturbances (urge symptomatol., urge incontinence, pollakiuria, Nycturia, and detrusor muscle instability). Such substances include e.g. forskolin, L-858051, adenyl cyclase toxin, xamoterol, denopamine, clenbuterol, procaterol, salbutamol, sameterol, formoterol, terbutaline, fenoterol, BRL 37344, ZD 7114, CPG 12177, CL 316243, ICI 215.001, pindolol, IBMX, methoxymethyl-IBMX, vinpocetin, vincamin, HA-588, calmodulin antagonists, EHNA, amrinone, OPC 3698, enoximone, milrinone, Ro 13-6438, siguazodan, HL 725, 8-Br-cGMP, 8-pCPT-cGMP, Sp-8-Br-cGMPS, PET GCMcP, CD-80.633, BRL 30892, SQ 20009, 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolopyridine, ZK 62711, Ro 20-1724,, RP 73401, RS 25344, SB 2074499, TVX 2706, zardaverine, 8-bromo-cAMP, and Sp-cAMPS.

IT **71774-13-5 142754-28-7**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(substances increasing the intracellular content of cAMP or stimulating activity of cAMP binding proteins for the treatment of illnesses of the bladder)

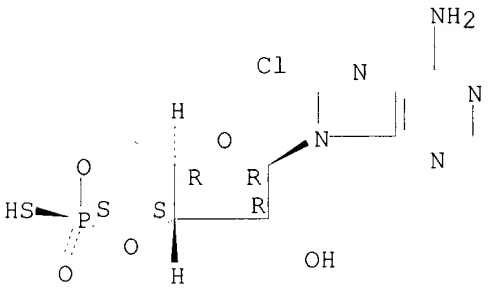
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2
REFERENCE(S): (1) Anon; HCAPLUS
(2) Anon; HCAPLUS

=> d ibib abs hitstr 2

L46 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:772398 HCAPLUS
DOCUMENT NUMBER: 133:344604
TITLE: Compositions and methods using a retinoid X receptor agonist and a protein kinase A activator for treatment of hyperproliferative diseases
INVENTOR(S): Benoit, Gerard; Gronemeyer, Hinrich; Lanotte, Michel; Gottardis, Marco
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA; Institut National de la Sante et de la Recherche Medicale; Centre National de la Recherche Scientifique; Universite Louis Pasteur
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064260	A1	20001102	WO 1999-US8908	19990423
W: AU, CA, JP, MX				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9941815	A1	20001110	AU 1999-41815	19990423

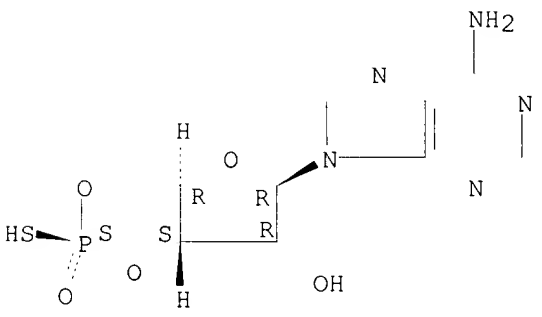
PRIORITY APPLN. INFO.: WO 1999-US8908 A 19990423

AB The invention provides compns. comprising a retinoid X receptor agonist and an agent capable of activating protein kinase A. The invention also provides methods of treating hyperproliferative diseases by administering a retinoid X receptor agonist and an agent capable of activating protein kinase A.

IT **71774-13-5**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(retinoid X receptor agonist and protein kinase A activator for treatment of hyperproliferative disease)

RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2
REFERENCE(S): (1) Fontana; J Natl Cancer Inst 1987, V78(6), P1107 HCAPLUS
(2) Huggenvik; Mol Endocrinol 1993, V7(4), P543

Searched by Susan Hanley STIC 305-4053

HCAPLUS

=> d ibib abs hitstr 3

L46 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:161140 HCAPLUS
DOCUMENT NUMBER: 132:203156
TITLE: Cyclic nucleotide-dependent protein kinase activators for promoters of neural regeneration
INVENTOR(S): Song, Hongjun; Poo, Mu-ming; Ming, Guo-li; Tessier-Lavigne, Marc; He, Zhigang
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012099	A1	20000309	WO 1999-US20139	19990902
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6268352	B1	20010731	US 1998-145820	19980902
AU 9957033	A1	20000321	AU 1999-57033	19990902
EP 1109561	A1	20010627	EP 1999-944061	19990902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

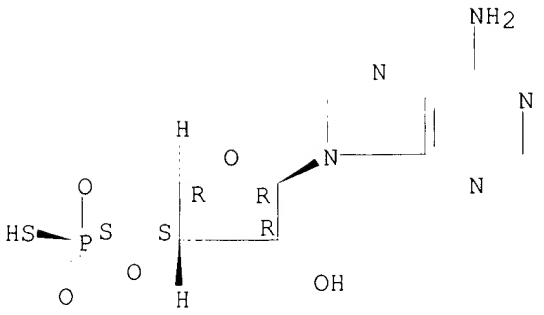
PRIORITY APPLN. INFO.: US 1998-145820 A 19980902
WO 1999-US20139 W 19990902

AB Methods and compns. are provided for promoting neural cell growth and/or regeneration. The general methods involve contacting with an activator of a cyclic nucleotide-dependent protein kinase a neural cell subject to growth repulsion mediated by a neural cell growth repulsion factor. The activator may comprise a direct or an indirect activator of the protein kinase; the repulsion factor typically comprises one or more natural, endogenous proteins mediating localized repulsion or inhibition of neural cell growth; and the target cells are generally vertebrate neurons, typically injured mammalian neurons. The subject compns. include mixts. comprising a neural cell, an activator of a cyclic nucleotide-dependent protein kinase, and a neural cell growth repulsion factor.

IT **71774-13-5 73208-40-9 127634-20-2**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cyclic nucleotide-dependent protein kinase activators for promoters of neural regeneration)

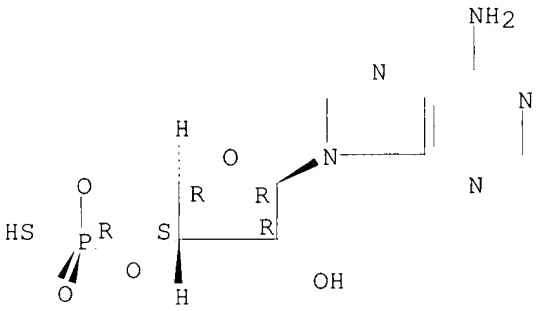
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



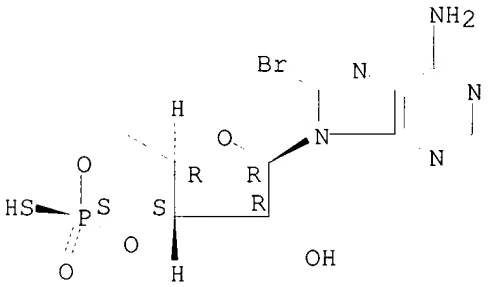
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2
REFERENCE(S):
(1) Genain, C; Proceedings of the National Academy of Sciences of the United States of America 1995, V92, P3601 HCAPLUS
(2) Rydel, R; Proceedings of the National Academy of Sciences of the United States of America 1988, V85, P1257 HCAPLUS

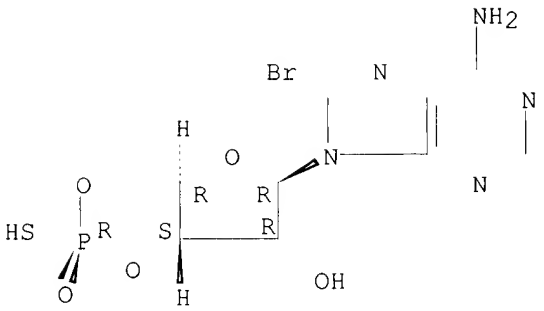
=> d ibib abs hitstr 4

L46 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:22669 HCAPLUS
DOCUMENT NUMBER: 132:333178
TITLE: Additive effects of IL-2 and protein kinase A type I antagonist on function of T cells from HIV-infected patients on HAART
AUTHOR(S): Aandahl, Einar Martin; Aukrust, Pal; Muller, Fredrik; Hanssen, Vidar; Tasken, Kjetil; Froland, Stig S.
CORPORATE SOURCE: Institute of Medical Biochemistry, University of Oslo, Oslo, N-0317, Norway
SOURCE: AIDS (London) (1999), 13(17), F109-F114
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to explore the basis for a possible immunomodulatory combination therapy with IL-2 and agents inhibiting protein kinase A (PKA) type I. Highly active antiretroviral therapy (HAART) has dramatically improved HIV therapy, but fails to eradicate the virus, and the persistence of HIV-assocd. immunodeficiency demonstrates the need for addnl. immunomodulating therapies. The authors have previously shown that hyperactivation of PKA type I inhibits the function of HIV-infected patient T cells. The sep. and combined effect of a PKA type I-selective antagonist (Rp-8-Br-cAMPS) and interleukin (IL)-2 on the function of T cells from HIV-infected patients on HAART was examd. The effect of Rp-8-Br-cAMPS on anti-CD3 stimulated proliferation and IL-2 prodn. and the combined effect with exogenous IL-2 were studied in vitro with cells from 13 HIV-infected patients on HAART and 6 uninfected controls. The PKA type I-selective antagonist improved cell proliferation (median 1.5-fold, maximal 2.8-fold) and IL-2 prodn. (median 1.5-fold, maximal 2.4-fold) in T cells from HIV-infected patients on HAART, but not in controls. The addn. of IL-2 enhanced proliferation of T cells from HIV-infected patients (approx. 1.9-fold) and that of controls (approx. 1.4-fold), but IL-2 had no effect at the concns. produced by treatment with PKA type I antagonist. However, the combined effect of IL-2 and PKA type I antagonist was additive and resulted in a further increase in T-cell proliferation (median 2.5-fold, maximal 5.8-fold), reaching levels comparable with those of uninfected controls in most of the patients. The authors' findings thus suggest a basis for a novel strategy in treatment of HIV infection by combining IL-2 therapy and treatment modalities counteracting PKA type I activity with HAART.

IT **129735-00-8**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(additive effects of interleukin-2 and protein kinase A type I antagonist on function of T cells from HIV-infected patients on HAART)
RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25

REFERENCE(S):
(1) Aandahl, E; FASEB J 1998, V12, P855 HCAPLUS
(2) Anastassiou, E; J Immunol 1992, V148, P2845 HCAPLUS
(3) Aukrust, P; Clin Exp Immunol 1992, V89, P211 HCAPLUS
(6) Chouaib, S; J Immunol 1985, V135, P1172 HCAPLUS
(7) Chun, T; Nature Med 1999, V5, P651 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 5

L46 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:670111 HCAPLUS
DOCUMENT NUMBER: 131:281568
TITLE: Method using a cAMP or cGMP analog, a phosphodiesterase inhibitor, or a nitric oxide precursor, donor, or analog for inducing vasorelaxation to treat pulmonary hypertension
INVENTOR(S): Lawson, Charles A.; Pinsky, David J.; Smerling, Arthur; Stern, David M.
PATENT ASSIGNEE(S): The Trustees of Columbia University In the City of New York, USA
SOURCE: U.S., 47 pp., Cont.-in-part of U. S. Ser. No.131,984.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968911	A	19991019	US 1997-362571	19970218
US 5728705	A	19980317	US 1993-131984	19931004
WO 9509636	A1	19950413	WO 1994-US11248	19941004

W: AU, CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

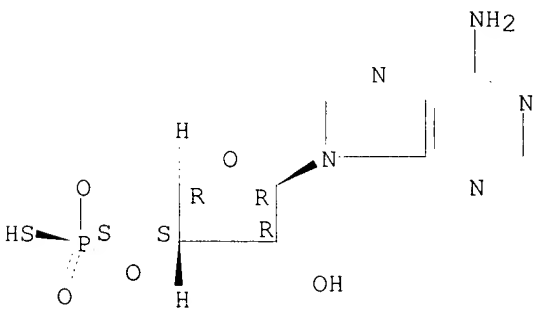
PRIORITY APPLN. INFO.: US 1993-131984 19931004
WO 1994-US11248 19941004

AB A method is provided for selectively decreasing pulmonary vascular resistance in a subject by administering endobronchially a drug chosen from among cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs.

IT **71774-13-5**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cAMP or cGMP analog, phosphodiesterase inhibitor, or nitric oxide precursor, donor, or analog for inducing vasorelaxation to treat pulmonary hypertension)

RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13
REFERENCE(S): (1) Afonso; US 5175151 1992 HCAPLUS
(2) Bagli; US 5250700 1993 HCAPLUS
(3) Brackett; Biochemical Pharmacology 1990, V39(12),

P1897 HCAPLUS
(4) Cowart; US 5362747 1994 HCAPLUS
(5) Duncia; US 5376666 1994 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 6

L46 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:184143 HCAPLUS
DOCUMENT NUMBER: 130:218318
TITLE: Use of purine nucleosides for modulating the axonal outgrowth of central nervous system neurons
INVENTOR(S): Benowitz, Larry I.
PATENT ASSIGNEE(S): Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911274	A1	19990311	WO 1998-US3001	19980220
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9866568	A1	19990322	AU 1998-66568	19980220
EP 1009412	A1	20000621	EP 1998-908565	19980220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001516695	T2	20011002	JP 2000-508376	19980220

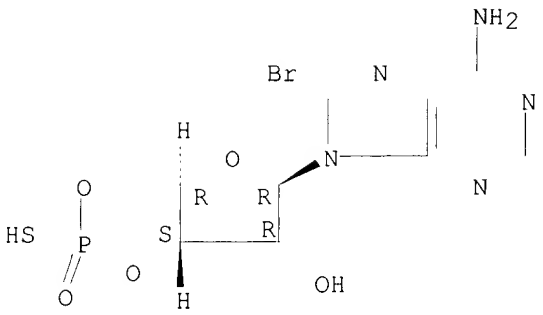
PRIORITY APPLN. INFO.: US 1997-921902 A2 19970902
WO 1998-US3001 W 19980220

AB Methods and compns. for modulating the axonal outgrowth of central nervous system neurons are provided. Methods for stimulating the axonal outgrowth of central nervous system neurons following an injury (e.g., stroke, Traumatic Brain Injury, cerebral aneurism, spinal cord injury and the like) and methods for inhibiting the axonal outgrowth of central nervous system neurons in conditions such as epilepsy, e.g., post-traumatic epilepsy, and neuropathic pain syndrome, are also provided. These methods generally involve contacting the central nervous system neurons with a purine nucleoside, or analog thereof. Preferably, inosine or guanosine is used to stimulate axonal outgrowth and 6-thioguanine is used to inhibit axonal outgrowth. The methods and compns. are particularly useful for modulating the axonal outgrowth of mammalian central nervous system neurons, such as mammalian retinal ganglion cells. Pharmaceutical and packaged formulations that include the purine nucleosides, and analogs thereof, of the invention are also provided.

IT **152322-58-2**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(purine nucleosides and analogs for modulating the axonal outgrowth of central nervous system neurons)

RN 152322-58-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5
REFERENCE(S):

(1) Greene, L; J NEUROSCI 1990, V10(5) HCAPLUS
(2) Gysbers, J; INT J DEV NEUROSCI 1996, V14(1) HCAPLUS
(3) Gysbers, J; NEUROREPORT 1992, V3(11), P997 HCAPLUS
(4) Medcament, P; WO 9400132 A 1994 HCAPLUS
(5) Svensson, B; EUR J NEUROSCI 1993, V5(8) MEDLINE

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L46 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:719272 HCAPLUS
DOCUMENT NUMBER: 130:490
TITLE: Use of compounds inhibiting cAMP-dependent protein kinase A as immunomodulating agents for treating immunosuppressive diseases
INVENTOR(S): Tasken, Kjetil; Aandahl, Einar Martin; Aukrust, Pal; Skalhegg, Bjorn S.; Muller, Fredrik; Froland, Stig; Hansson, Vidar
PATENT ASSIGNEE(S): Norway
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9848809	A1	19981105	WO 1998-NO134	19980429
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9870865	A1	19981124	AU 1998-70865	19980429
EP 1024809	A1	20000809	EP 1998-917808	19980429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 9905269	A	19991213	NO 1999-5269	19991028

PRIORITY APPLN. INFO.: NO 1997-1997 A 19970429
WO 1998-NO134 W 19980429

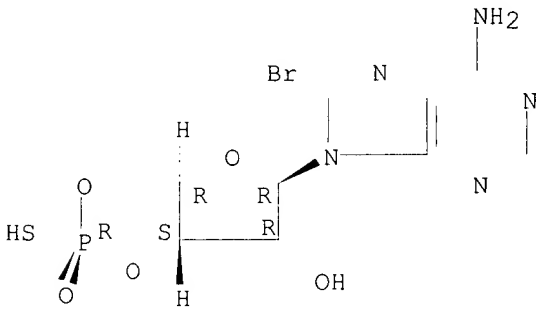
AB Several compds. capable of inhibiting cAMP-dependent protein kinase A (PKA) are used to produce a medicament increasing T-cell proliferation in patients with immunosuppressive diseases. Inhibitors include cAMP analogs, ribozymes, antisense DNA, and peptides binding to the anchoring region of PKA. In T-cells from normal blood donors, TCR/CD3-stimulated T-cell proliferation was inhibited by a cAMP agonist (Sp-8-Br-cAMPS). This effect was almost completely reversed by increasing concns. of complementary antagonist (Rp-8-Br-cAMPS (I)). However, antagonist alone did not alter proliferation of normal T-cells. In contrast, when the TCR/CD3-induced proliferation of T-cells from a HIV-infected patient was investigated, I not only reversed the effect of the complementary agonist, but further increased the proliferation above the levels in untreated cells. When the effect of the antagonist alone was assessed in T-cells from HIV-infected patients, there was a concn.-dependent increase in TCR/CD3-induced proliferation that was more than 2-fold at higher concns. T-cells responding poorly to TCR/CD3 stimulation benefitted most from cAMP antagonist treatment.

IT **129735-00-8 129735-01-9 142754-27-6**
156816-36-3 215597-30-1 215597-33-4
RL: BPR (Biological process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(as cAMP antagonist; cAMP-dependent protein kinase A inhibitors as immunomodulating agents for treating immunosuppressive diseases)

RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI)

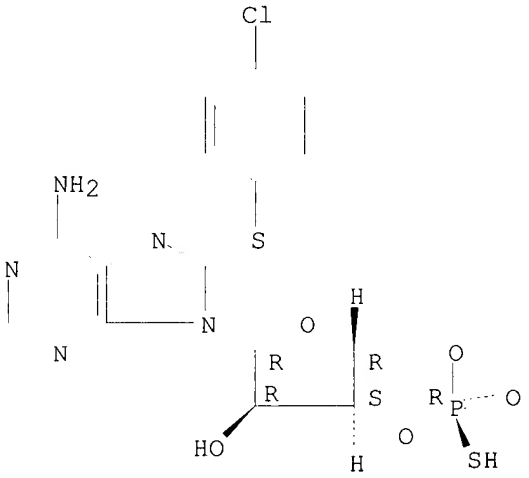
(CA INDEX NAME)

Absolute stereochemistry.



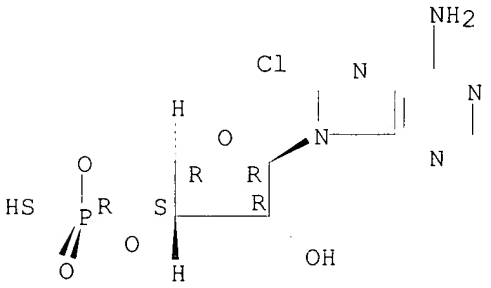
RN 129735-01-9 HCAPLUS
CN Adenosine, 8-[(4-chlorophenyl)thio]-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



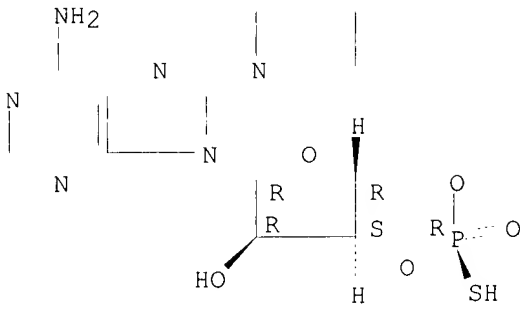
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



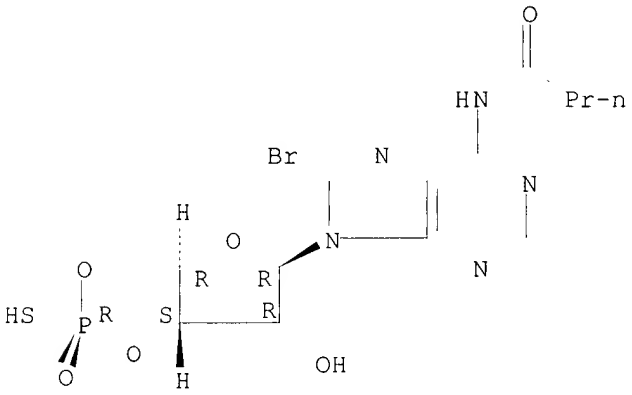
RN 156816-36-3 HCAPLUS
CN Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



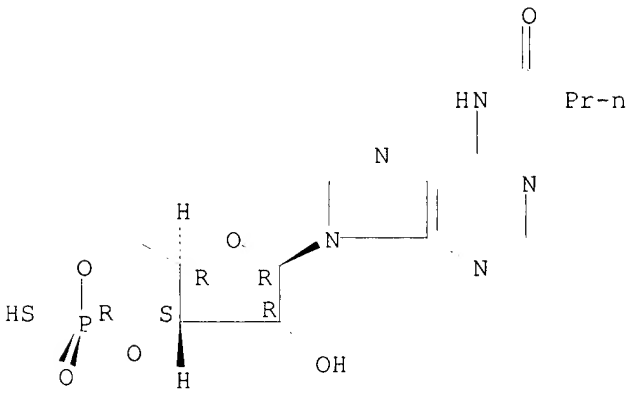
RN 215597-30-1 HCAPLUS
CN Adenosine, 8-bromo-N-(1-oxobutyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 215597-33-4 HCAPLUS
CN Adenosine, N-(1-oxobutyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5
REFERENCE(S): (1) Hybridon Inc; WO 9711171 A1 1997 HCAPLUS

(2) Icos Corporation; WO 9704096 A1 1997 HCAPLUS
(3) The Regents Of The University Of California; WO 9319766 A1 1993 HCAPLUS
(4) The Secretary Department Of Health And Human Services; WO 9321929 A1 1993 HCAPLUS
(5) University Research Corporation; WO 9416736 A1 1994 HCAPLUS

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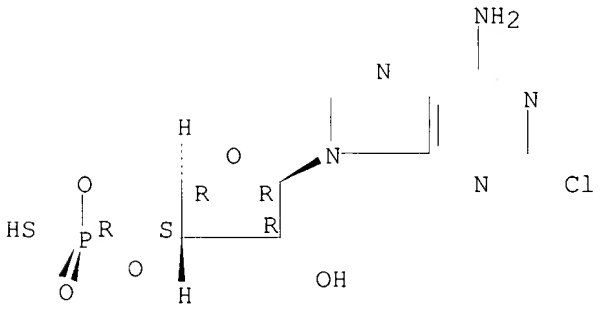
L46 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:572406 HCAPLUS
DOCUMENT NUMBER: 129:285575
TITLE: Quantitative structure-activity relations for the relative affinities of cAMP derivatives with large substituents in positions 2 and 8 for the four different regulatory sites of a protein kinase
AUTHOR(S): Liauw, Susanne; Iwitzki, Franz; Muresan, Sorel; Bologa, Cristian; Chiriac, Adrian; Kurunczi, Ludovic; Simon, Zeno; Jastorff, Bernd
CORPORATE SOURCE: Dep. Bioorganic Chem., Univ. Bremen, Bremen, D-2000, Germany
SOURCE: Rev. Roum. Chim. (1998), 43(3), 241-253
CODEN: RRCHAX; ISSN: 0035-3930
PUBLISHER: Editura Academiei Romane
DOCUMENT TYPE: Journal
LANGUAGE: English

AB QSAR's by the MTD-method for a series of 32 derivs. of cAMP with large substituents in position 8 and for a series of 21 derivs. with large substituents in position 2 are obtained. Thiophosphoric acid derivs. are also included. As structural parameters, the relative nitrogen base lipophilicity, the presence of an equatorial or axial S atom and the presence of aliph. amino group, protonated at pH = 7 are considered. Satisfactory correlational results, including a cross-validation like procedure, are obtained in most cases. The results emphasize structural features important for binding to four sites (AI, BI, AII, and BII) of two different protein phosphokinases (cAKI and cAKII). The synthesis and characterization of eight new compds. are also described.

IT **124844-92-4 124854-63-3 142754-27-6**
142754-28-7 156816-35-2 156816-36-3,
Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-(hydrogen phosphorothioate), (R)- **214272-09-0 214272-10-3 214276-87-6**
214276-94-5
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(quant. structure-activity relations for the relative affinities of cAMP derivs. for protein kinase regulatory sites)

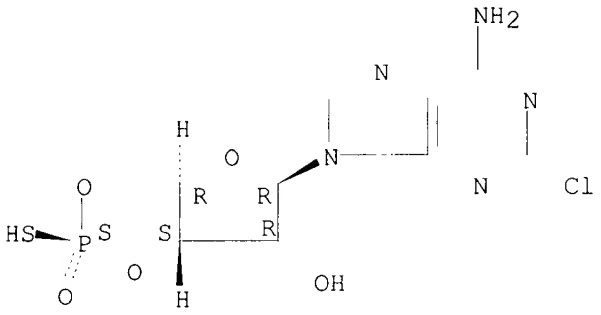
RN 124844-92-4 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(R)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



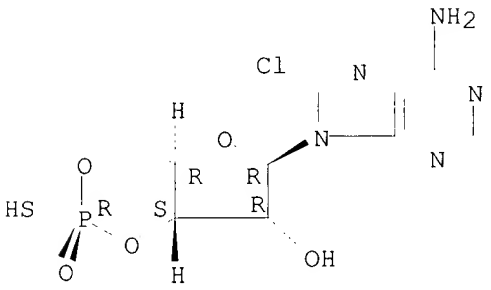
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



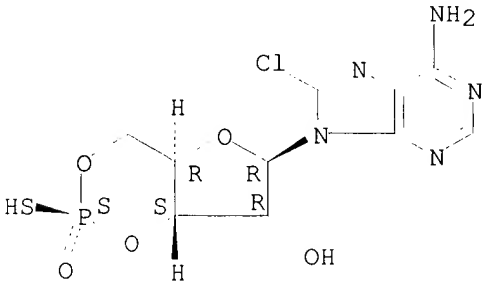
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



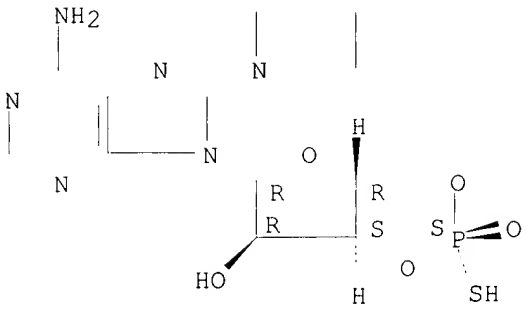
RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



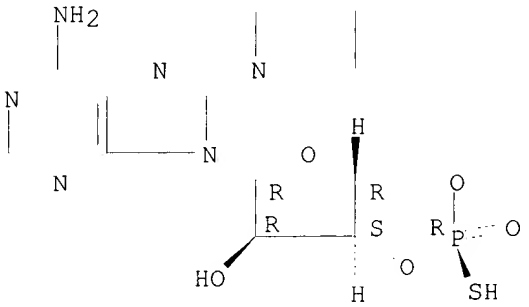
RN 156816-35-2 HCAPLUS
CN Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



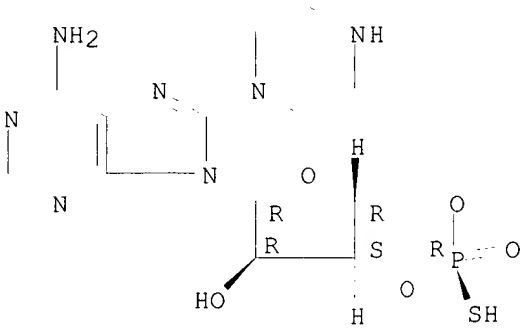
RN 156816-36-3 HCAPLUS
CN Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



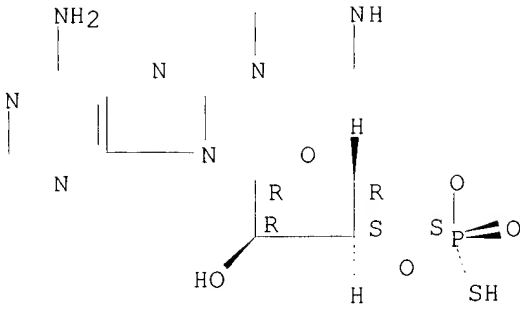
RN 214272-09-0 HCAPLUS
CN Adenosine, 8-(1-piperazinyl)-, cyclic 3',5'-[(R)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



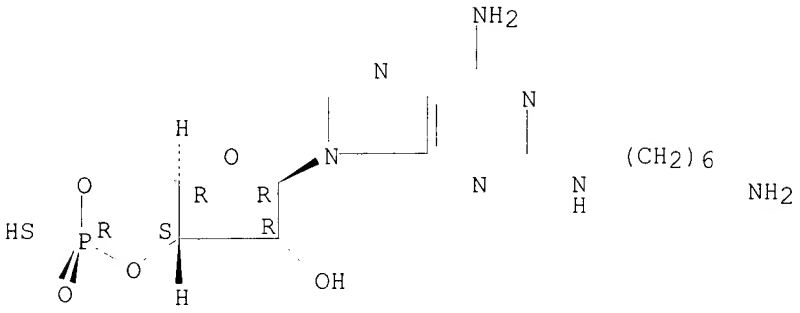
RN 214272-10-3 HCAPLUS
CN Adenosine, 8-(1-piperazinyl)-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



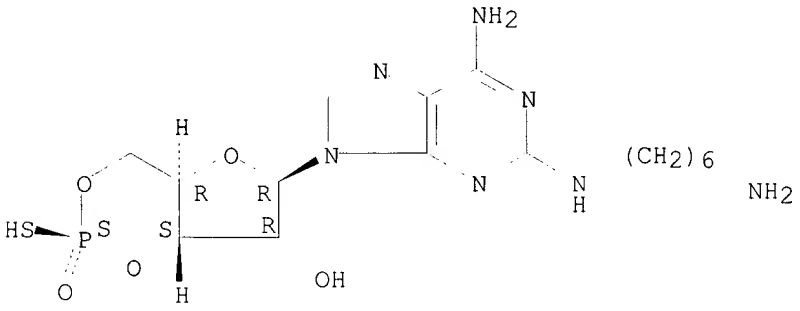
RN 214276-87-6 HCAPLUS
CN Adenosine, 2-[(6-aminohexyl)amino]-, cyclic 3',5'-[(R)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 214276-94-5 HCAPLUS
CN Adenosine, 2-[(6-aminohexyl)amino]-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



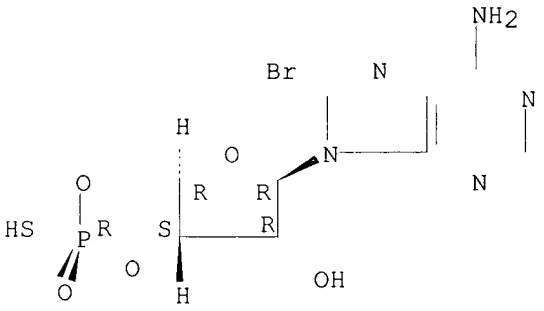
=> d ibib abs hitstr 9

L46 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:434799 HCAPLUS
DOCUMENT NUMBER: 129:170140
TITLE: Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients
AUTHOR(S): Aandahl, Einar Martin; Aukrust, Pal; Skalhegg, Bjorn S.; Muller, Fredrik; Froland, Stig S.; Hansson, Vidar; Tasken, Kjetil
CORPORATE SOURCE: Institute of Medical Biochemistry, University of Oslo, Oslo, N-0317, Norway
SOURCE: FASEB J. (1998), 12(10), 855-862
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CAMP-dependent protein kinase A (PKA) type I has been established as an acute inhibitor of T cell activation. For this reason, we investigated the possible role of PKA type I in HIV-induced T cell dysfunction. T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analog than are normal T cells. A PKA type I-selective antagonist increases the impaired proliferation of T cells from HIV-infected patients to normal or subnormal levels (up to 2.8-fold). Follow-up of patients after initiation of highly active antiretroviral treatment revealed that a majority of patients have a persistent T cell dysfunction that is normalized by incubation of T cells with Rp-8-Br-cAMPS. These observations imply that increased activation of PKA type I may contribute to the progressive T cell dysfunction in HIV infection and that PKA type I may be a potential target for immunomodulating therapy.

IT **129735-00-8**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients)
RN 129735-00-8 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 10

L46 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:169417 HCAPLUS
DOCUMENT NUMBER: 128:226257
TITLE: Compositions and methods modulating amyloid precursor protein for treatment of neurological disorders and neurodegenerative diseases, including Alzheimer's disease
INVENTOR(S): Lee, Robert K. K.; Wurtman, Richard J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809523	A1	19980312	WO 1997-US15321	19970905
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1006798	A1	20000614	EP 1997-941386	19970905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1996-25507 P 19960905
US 1997-33765 P 19970115
WO 1997-US15321 W 19970905

AB It has been discovered that the stimulation of .beta.-adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes. Hence, the in vitro or in vivo exposure of neuronal cells to certain compns. comprising .beta.-adrenergic receptor ligands or agonists, including, e.g., norepinephrine, isoproterenol and the like, increases APP mRNA transcription and consequent APP overprodn. These increases are blocked by .beta.-adrenergic receptor antagonists, such as propranolol. The in vitro or in vivo treatment of these cells with 8Br-cAMP, prostaglandin E2 (PG E2), forskolin, and nicotine ditartrate also increased APP synthesis, including an increase in mRNA and holoprotein levels, as well as an increase in the expression of glial fibrillary acidic protein (GFAP). Compns. and methods are disclosed of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of .beta.-adrenergic receptors. It has further been found that the increase in APP synthesis caused by 8Br-cAMP, PG E2, forskolin, or nicotine ditartrate is inhibited by immunosuppressants or anti-inflammatory agents, such as cyclosporin A, and FK-506 (tacrolimus), as well as ion-channel modulators, including ion chelating agents such as EGTA, or calcium/calmodulin kinase inhibitors, such as KN93. The present invention has broad implications in the alleviation, treatment, or prevention of neurol. disorders and neurodegenerative diseases, including Alzheimer's disease.

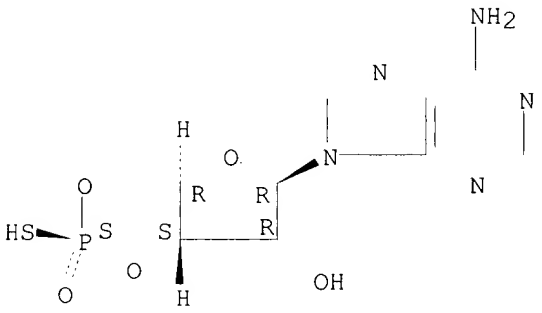
IT **93602-66-5**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(amyloid precursor protein modulation in treatment of neurol. and neurodegenerative diseases, including Alzheimer's disease)

RN 93602-66-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate], compd. with N,N-diethylethanamine (1:1) (9CI) (CA INDEX NAME)

CM 1

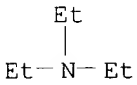
CRN 71774-13-5
CMF C10 H12 N5 O5 P S
CDES 5:B-D-RIBO-3(S)

Absolute stereochemistry.



CM 2

CRN 121-44-8
CMF C6 H15 N



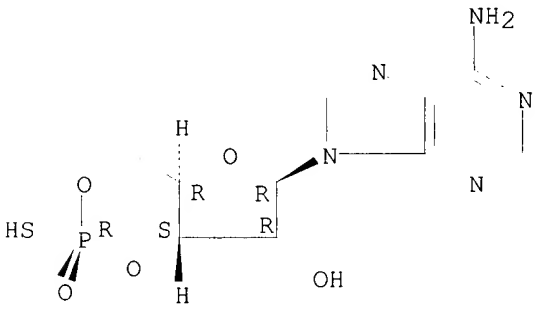
=> d ibib abs hitstr 11

L46 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:419349 HCAPLUS
DOCUMENT NUMBER: 127:75941
TITLE: Protein kinase A inhibitor attenuates levodopa-induced motor response alterations in the hemi-parkinsonian rat
AUTHOR(S): Oh, Justin D.; Del Dotto, Paolo; Chase, Thomas N.
CORPORATE SOURCE: Experimental Therapeutics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Neurosci. Lett. (1997), 228(1), 5-8
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chronic administration of levodopa, the std. treatment for Parkinson's disease, is ultimately assocd. with disabling alterations in motor response. To evaluate the possible contribution of striatal cAMP-dependent protein kinase A (PKA) signaling pathways to these response modifications, the acute effects of a PKA inhibitor, Rp-cAMPS (Rp-diastereoisomer of adenosine cyclic 3',5'-phosphorothioate), on motor response changes attending chronic, twice-daily administration of levodopa were measured in 6-hydroxydopamine-lesioned hemi-parkinsonian rats. A single intrastriatal injection of Rp-cAMPS (2.5 or 25 .mu.g) dose-dependently attenuated both the shortened duration and augmented intensity of levodopa-induced turning. Rp-cAMPS completely normalized motor responses to a dopamine D1 agonist (SKF 38392), but had no effect on those to a dopamine D2 agonist (quinpirole). These results suggest that D1 receptor-mediated PKA activation may contribute to the development of the altered motor responses assocd. with chronic levodopa treatment.

IT **73208-40-9**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(parkinson-like motor response alterations induced by chronic levodopa attenuation by)
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 12

L46 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:165500 HCAPLUS
DOCUMENT NUMBER: 126:166497
TITLE: Method and composition for treating cystic fibrosis
INVENTOR(S): Drumm, Mitchell L.; Kelley, Thomas J.
PATENT ASSIGNEE(S): Case Western Reserve University, USA
SOURCE: U.S., 10 pp. Cont.-in-part of U.S. Ser. No. 299,013, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5602110	A	19970211	US 1995-378638	19950126
WO 9606612	A1	19960307	WO 1995-US11008	19950829
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9535415	A1	19960322	AU 1995-35415	19950829

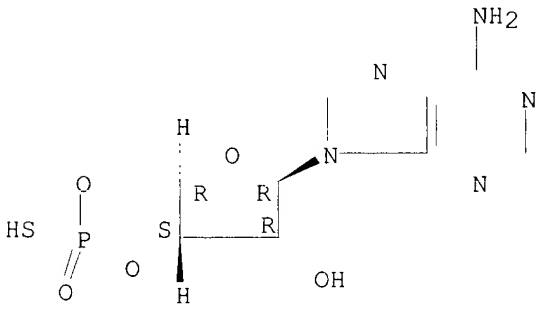
PRIORITY APPLN. INFO.: US 1994-299013 19940831
US 1995-378638 19950126
WO 1995-US11008 19950829

AB Cystic fibrosis is treated by administering to a patient a first component, a second component, and preferably a third component. The first component is an inhibitor which is specific for a cGMP-inhibited type III cAMP phosphodiesterase, preferably milrinone or amrinone; the second component is an adenylate cyclase activator, preferably forskolin, isoproterenol or albuterol; the third component is cAMP or a cAMP analog which activates protein kinase A. The components are administered by aerosolization or nebulization. Cystic fibrosis transmembrane conductance regulator-mediated chloride permeability is activated in cystic fibrosis cells by the synergistic action of an adenylate cyclase activator and a type III phosphodiesterase inhibitor.

IT **23645-17-2**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(aerosols contg. cAMP phosphodiesterase inhibitor and adenylate cyclase activator and protein kinase A activator for treatment of cystic fibrosis)

RN 23645-17-2 HCAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphorothioate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 13

L46 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:113512 HCAPLUS
DOCUMENT NUMBER: 124:156073
TITLE: cAMP derivatives as synovial membrane cell proliferation inhibitors and pharmaceutical compositions containing cAMP derivatives for treatment of chronic arthrorheumatism
INVENTOR(S): Higaki, Megumi; Sakane, Takeshi; Mizushima, Yutaka; Yasumoto, Takashi; Morisawa, Yoshitomi
PATENT ASSIGNEE(S): Ltt Inst Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

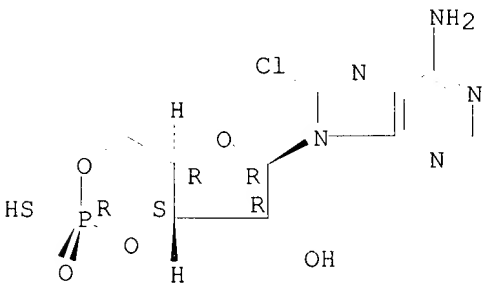
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07324035	A2	19951212	JP 1994-116194	19940530

AB CAMP derivs. as synovial membrane cell proliferation inhibitors and pharmaceutical compns. contg. CAMP derivs. for treatment of chronic arthrorheumatism are claimed. The compds. markedly inhibited the proliferation of synovial membrane cells in cultures. Capsules were formulated contg. 8-chloro-cAMP 5.mu.g, lactose 148, corn starch 50, and magnesium stearate 1.5g.

IT **142754-27-6 142754-28-7**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cAMP derivs. as synovial membrane cell proliferation inhibitors and pharmaceutical compns. contg. CAMP derivs. for treatment of chronic arthrorheumatism)

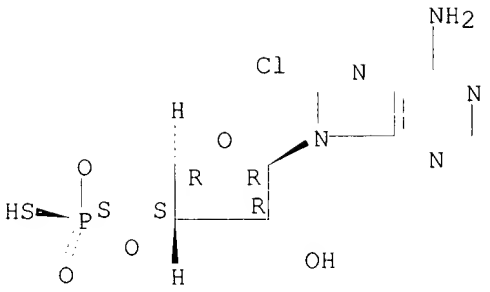
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.


NH2
Cl
N
N
N
N
H
O
O
R
R
R
HS
P
S
S
O
O
H
OH

=> d ibib abs hitstr 14

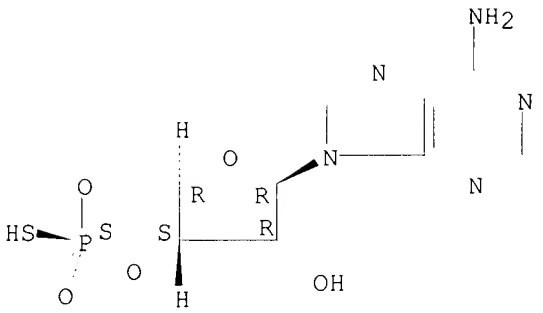
L46 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:656486 HCAPLUS
DOCUMENT NUMBER: 123:131990
TITLE: Evidence for several pathways of biological response to hydrolyzable cAMP-analogs using a model system of apoptosis in IPC-81 leukemia cells
AUTHOR(S): Ruchaud, S.; Zorn, M.; Davilar-Villar, E.; Genieser, H. G.; Hoffmann, C.; Gjersten, B. T.; Doeskeland, S. O.; Jastorff, B.; Lanoote, M.
CORPORATE SOURCE: Centre G. Hayfem, Hopital St-Louis, Paris, Fr.
SOURCE: Cell. Pharmacol. (1995), 2(3), 127-40
CODEN: CEPHEG; ISSN: 1351-3214
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Degradable and undegradable cAMP analogs with a wide range of rationally selected (testkit concept) chem. modifications were studied for their apoptotic potency in the rat IPC-81 model for acute myelocytic leukemia. The biol. activity of corresponding 5'AMP and adenosine metabolites was compared. To discriminate a cA-kinase response from non-kinase effects the authors used a subclone of the IPC-81 line with a sub-responsiveness to cA-kinase I activation by cAMP analogs. As proven by HPLC, only cAMP analogs with an axial (Sp) and equatorial (Rp) substitution at the phosphate moiety were partially or totally resistant against metab. in cell culture. Heat inactivation of serum only reduced but not prevented the formation of metabolites. The results gave different dose responses due to the type of modification at the signal mols. and the type of cell line. Undegradable cAMP analogs only induced apoptosis via the cA-kinase pathway in the two cell lines; most efficiently through the highly lipophilic, resistant and cA-kinase specific analog Sp-DCl-cBIMPS. The lipophilic cAMP antagonist Rp-8Cl-cAMPS inhibited the induction of apoptosis by its corresponding Sp-8Cl-cAMPS in a dose-dependent manner. Degradable cAMP analogs act via the cyclic nucleotides and/or their metabolites. Rationale for the different types of responses based on structure activity relations are discussed and mechanisms of actions are proposed. The authors' study supports an essential participation of the cAMP signaling pathway in induction of apoptosis, if a highly cooperative way of cell death is induced. Exclusively via the cAMP signaling cascade, an analog will act only if the deriv. is undegradable, highly membrane permeable and a potent cA-kinase activator. Degradable analogs exhibit their effects through diverse mechanisms. Detailed biochem. and cell biol. studies with the complete set of catabolites and metabolites of those derivs., which exhibit the highest activity, allow the design of a new generation of nucleosides and nucleotides with high, hopefully cell type selective, potential for apoptosis in tumor cells.

IT **71774-13-5 73208-40-9 124854-63-3**, Adenosine, 2-chloro-, cyclic 3',5'-(hydrogen phosphorothioate), (S)-
127634-20-2 142754-27-6 142754-28-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(evidence for several pathways of biol. response to hydrolyzable cAMP-analogs using a model system of apoptosis in IPC-81 leukemia cells)

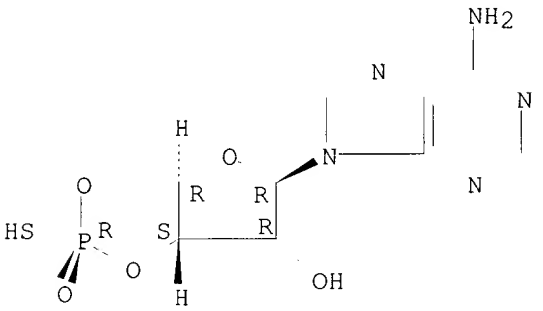
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



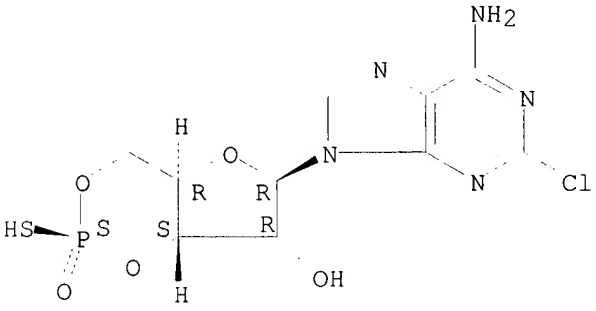
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



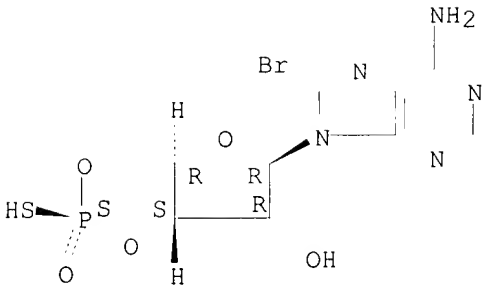
RN 124854-63-3 HCAPLUS
CN Adenosine, 2-chloro-, cyclic 3',5'-[(S)-hydrogen phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



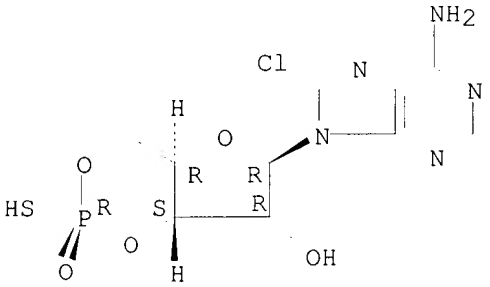
RN 127634-20-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



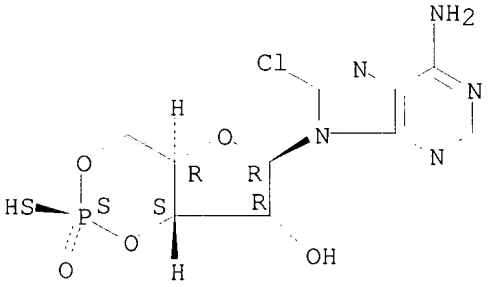
RN 142754-27-6 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 142754-28-7 HCAPLUS
CN Adenosine, 8-chloro-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 15

L46 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:603959 HCAPLUS
DOCUMENT NUMBER: 123:17877
TITLE: Method of inducing vasorelaxation to treat pulmonary hypertension
INVENTOR(S): Lawson, Charles A.; Pinsky, David J.; Smerling, Arthur; Stern, David M.
PATENT ASSIGNEE(S): Trustees of Columbia University in the City of New York, USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509636	A1	19950413	WO 1994-US11248	19941004
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5728705	A	19980317	US 1993-131984	19931004
AU 9479652	A1	19950501	AU 1994-79652	19941004
US 5968911	A	19991019	US 1997-362571	19970218

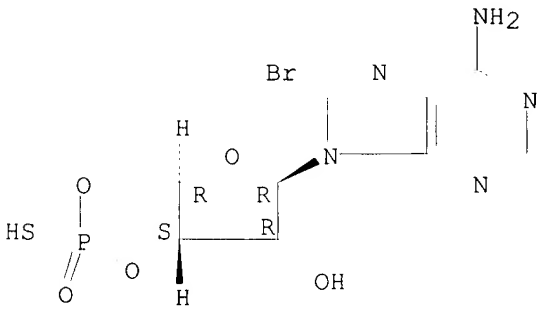
PRIORITY APPLN. INFO.: US 1993-131984 19931004
WO 1994-US11248 19941004

AB A method of selectively decreasing pulmonary vascular resistance in a subject comprises administering endobronchially a drug chosen from cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs, as aerosol solns. or powders.

IT **152322-58-2**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(aerosols contg. vasorelaxants for treatment of pulmonary hypertension)

RN 152322-58-2 HCAPLUS
CN Adenosine, 8-bromo-, cyclic 3',5'-(hydrogen phosphorothioate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



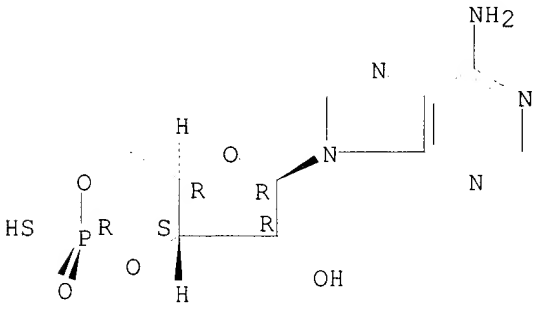
=> d ibib abs hitstr l44 1

L44 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:976166 HCAPLUS
DOCUMENT NUMBER: 124:49142
TITLE: (RP)-cAMPS inhibits the **cAMP-dependent protein kinase** by blocking the cAMP-induced conformational transition
AUTHOR(S): Dostmann, Wolfgang R. G.
CORPORATE SOURCE: Institut fuer Pharmakologie und Toxikologie, Technische Universitaet Muenchen, Biedersteiner Str. 29, 80802, Muenchen, Germany
SOURCE: FEBS Lett. (1995), 375(3), 231-4
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (RP)-cAMPS is known to inhibit competitively the cAMP-induced activation of **cAMP-dependent protein kinase** (PKA). The mol. nature of this inhibition, however, is unknown. By monitoring the intrinsic tryptophan fluorescence of recombinant **type I** regulatory subunit of PKA under unfolding conditions, a free energy value (.DELTA.GDH2O) of 8.23 kcal/mol was calcd. The cAMP-free form of the regulatory subunit was less stable with .DELTA.GDH2O = 6.04 kcal/mol. Native stability was recovered by treatment of the cAMP-free protein with either cAMP or (SP)-cAMPS but not with (RP)-cAMPS. Thus, (RP)-cAMPS binding to the regulatory subunit keeps the protein in a locked conformation, unable to release the catalytic subunit. This finding was further supported by demonstrating that holoenzyme formation was greatly accelerated only when bound cAMP was replaced with (RP)-cAMPS but not with cAMP or (SP)-cAMPS.

IT **73208-40-9**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
((RP)-cAMPS inhibits **cAMP-dependent protein kinase** by blocking cAMP-induced conformational transition)
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **142008-29-5, Protein kinase A**
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process)
((RP)-cAMPS inhibits **cAMP-dependent protein kinase** by blocking cAMP-induced conformational transition)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

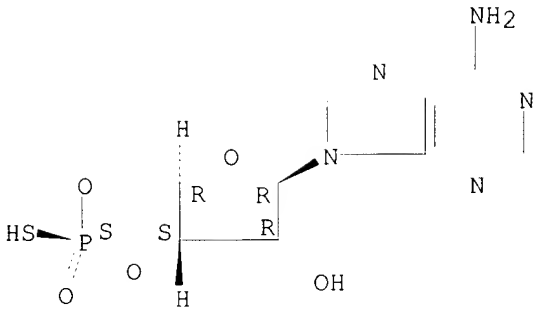
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr l44 2

L44 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:502990 HCAPLUS
DOCUMENT NUMBER: 121:102990
TITLE: (Rp)- and (Sp)-8-piperidino-adenosine 3',5'-(cyclic)thiophosphates discriminate completely between site A and B of the regulatory subunits of **cAMP-dependent protein kinase type I** and II
AUTHOR(S): Oegreid, Dagfinn; Dostmann, Wolfgang; Genieser, Hans-Gottfried; Niemann, Percy; Doeskeland, Stein Ove; Jastorff, Bernd
CORPORATE SOURCE: Cent. Mol. Med., Univ. Bergen, Norway
SOURCE: Eur. J. Biochem. (1994), 221(3), 1089-94
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 8-Piperidino-cAMP has previously been shown to bind with high affinity to cAMP-binding site A of the regulatory subunit of **cAMP-dependent protein kinase** (**protein kinase A**) **type I** (AI), whereas it is partially excluded from the homologous site (AII) of isoenzyme II. To further increase this selectivity, the (Rp)- and (Sp)-diastereoisomers of 8-piperidinoadenosine 3',5'-(cyclic)thiophosphate (8-piperidino-cAMP[S]) were synthesized and analyzed for their potency to inhibit the binding of [3H]cAMP to sites A and B from **type I** (rabbit skeletal muscle) and type II (bovine myocardium) **protein kinases A**. (Sp)-8-Piperidino-cAMP[S] showed an enhanced relative affinity for site AI, thus being by far the best A-selective compd. (>100-fold) tested for this isoenzyme. In contrast, the (Rp)-isomer was less selective for AI than 8-piperidino-cAMP itself. The redn. in affinities for BII, compared to 8-piperidino-cAMP, were 10- and 50-fold for the (Sp)- and (Rp)-isomers, resp. Both isomers were almost completely excluded from AII, with affinities .apprx.1000-fold lower than 8-piperidino-cAMP itself. The (Rp)-isomer selected BII with an affinity .apprx.10,000-fold higher than for AII, whereas the (Sp)-isomer showed a preference of .apprx.70,000-fold in favor of BII. 8-Piperidino-cAMP as well as its (Sp)-isomer activated both types of holoenzyme protein kinases whereas the (Rp)-isomer acted as an antagonist of cAMP-induced activation. It was concluded that the combination of piperidino- and exocyclic S substitutions generate cAMP analogs that completely discriminate between sites A and B of **protein kinases A**.
IT **142008-29-5, Protein kinase A**
RL: BIOL (Biological study)
(I and II, discrimination between cAMP-binding sites A and B of regulatory subunit of, with piperidino-cAMP thiophosphate diastereomers)
RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

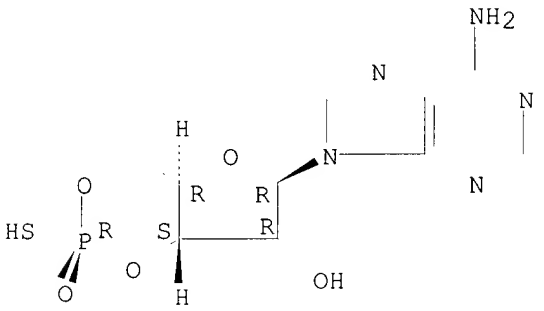
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **71774-13-5 73208-40-9**
RL: PROC (Process)
(conversion of, to piperidino-cAMP thiophosphate)
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



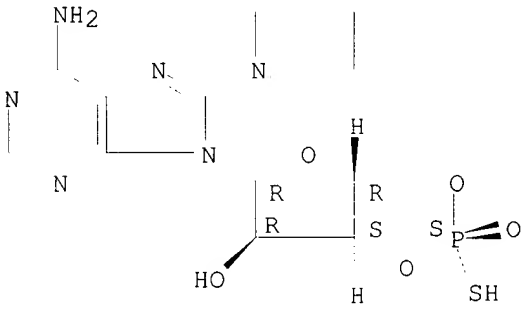
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



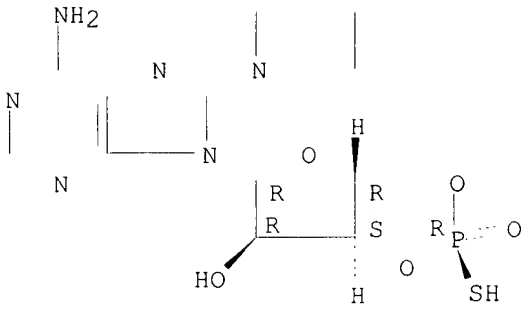
IT **156816-35-2P 156816-36-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **protein kinase A** regulatory subunit binding of, discrimination between cAMP-binding sites A and B in relation to)
RN 156816-35-2 HCAPLUS
CN Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156816-36-3 HCAPLUS
CN Adenosine, 8-(1-piperidinyl)-, cyclic 3',5'-[hydrogen (R)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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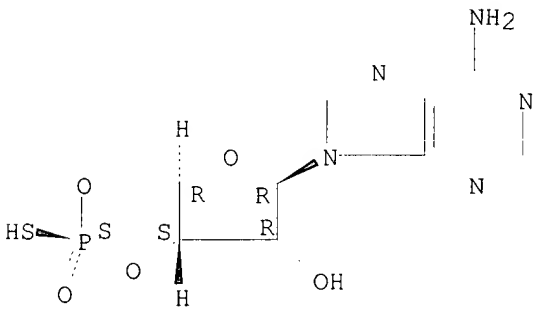
=> d ibib abs hitstr l44 3

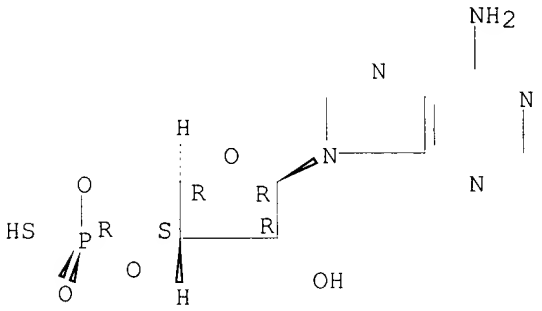
L44 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:509198 HCAPLUS
DOCUMENT NUMBER: 115:109198
TITLE: Identifying the molecular switches that determine whether (Rp)-cAMPS functions as an antagonist or an agonist in the activation of **cAMP-dependent protein kinase** I
AUTHOR(S): Dostmann, Wolfgang R. G.; Taylor, Susan S.
CORPORATE SOURCE: Dep. Chem., Univ. California, San Diego, La Jolla, CA, 92093-0654, USA
SOURCE: Biochemistry (1991), 30(35), 8710-16
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous investigations revealed that under physiol. conditions in the presence of MgATP the phosphorothioate analog of cAMP, (Rp)-cAMPS, is a competitive inhibitor and antagonist for cAMP for **cAMP-dependent protein kinases** I and II. For the **type I** holoenzyme, the antagonist properties of (Rp)-cAMPS were shown here to be absolutely dependent on MgATP. In the absence of MgATP, (Rp)-cAMPS serves as a weak agonist with an activation const. of of 7.9 .mu.M. The high-affinity binding of MgATP imposes a barrier on cAMP-induced activation of the holoenzyme, a barrier that both cAMP and (Sp)-cAMPS, but not (Rp)-cAMPS can overcome. In the absence of MgATP, this barrier no longer exists, and (Rp)-cAMPS functions as an agonist. The holoenzyme also was formed with mutant regulatory subunits. Replacing the essential arginine, predicted to bind the exocyclic O atoms of cAMP, in site A with lysine abolishes high-affinity binding of cAMP to site A. The holoenzyme formed with this mutant R subunit is activated by (Rp)-cAMPS in both the presence and absence of MgATP. These results suggest that the stereospecific requirements for holoenzyme activation involve this guanidinium side-chain. Mutations that eliminate the high-affinity binding of MgATP, such as the introduction of an autophosphorylation site in the autoinhibitory domain, also generate a holoenzyme that can be activation by (Rp)-cAMPS. In the case of the type II holoenzyme, (Rp)-cAMPS is an antagonist in both the presence and absence of MgATP, emphasizing distinct roles for MgATP in these 2 forms of **cAMP-dependent protein kinase.**
IT **71774-13-5**
RL: BIOL (Biological study)
(protein kinase cAMP-dependent form of heart activation by, kinetics of)
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **73208-40-9**
RL: BIOL (Biological study)
(protein kinase of heart activation by cAMP response to, as agonist or antagonist, magnesium-ATP in relation to)
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr l44 4

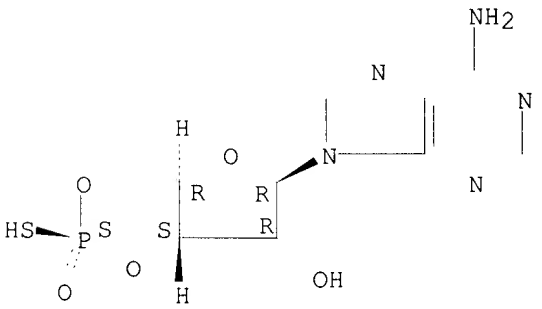
L44 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:511412 HCAPLUS
DOCUMENT NUMBER: 113:111412
TITLE: Inhibition of cGMP-dependent protein kinase by (Rp)-guanosine 3',5'-monophosphorothioates
AUTHOR(S): Butt, Elke; Van Bemmelen, Michael; Fischer, Lilo; Walter, Ulrich; Jastorff, Bernd
CORPORATE SOURCE: Fachbereich Chem., Univ. Bremen, Bremen, D-2800/33, Fed. Rep. Ger.
SOURCE: FEBS Lett. (1990), 263(1), 47-50
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The activation of the cGMP-dependent protein kinase of bovine lung and **cAMP-dependent protein kinase** of bovine heart by the diastereomers of guanosine 3',5'-monophosphorothioate, (Sp)-cGMPS and (Rp)-cGMPS, and 8-chloroguanosine 3',5'-monophosphorothioate, (Sp)-8-Cl-cGMPS and (Rp)-8-Cl-cGMPS, was investigated using the peptide, Kemptide, as substrate. The (Sp)-diastereomers, which have an axial exocyclic S atom, bound to the cGMP-dependent protein kinase and stimulated its phosphotransferase activity. In contrast, the (Rp)-isomers, which have an **equatorial** exocyclic S atom, bound to the enzyme without stimulation of its activity. (RP)-cGMPS and (Rp)-8-Cl-cGMPS antagonized the activation of the cGMP-dependent protein kinase with a K1 of 20 and 1.5 .mu.M, resp. (RP)-cGMPS also antagonized the activation of **cAMP-dependent protein kinase** with a Ki of 20 .mu.M. In contrast, (Rp)-8-Cl-cGMPS was a weak inhibitor of the **cAMP-dependent protein kinase** with a Ki of 100 .mu.M. (Rp)-8-Cl-cGMPS appeared to be a rather selective inhibitor of the cGMP-dependent protein kinase and may be a useful tool for studying the role of cGMP in broken and intact cell systems.

IT **71774-13-5 73208-40-9**
RL: BIOL (Biological study)
(protein kinases of heart and lung inhibition by, kinetics of)

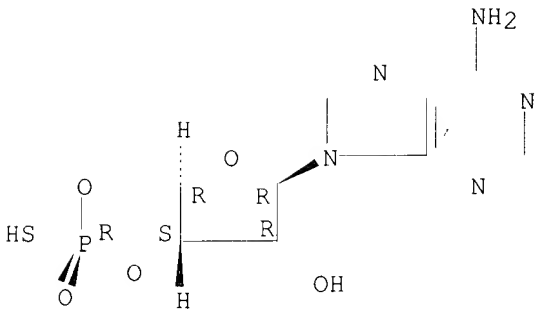
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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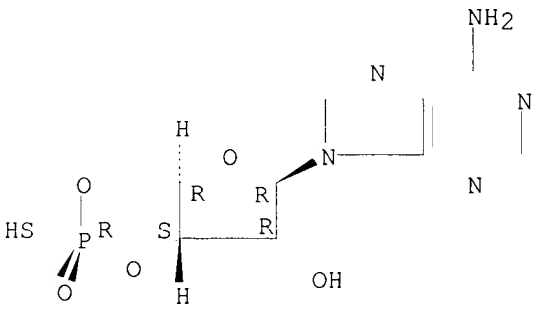
=> d ibib abs hitstr l44 5

L44 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:434359 HCAPLUS
DOCUMENT NUMBER: 109:34359
TITLE: Inhibition of **cAMP-dependent protein kinase** by adenosine cyclic 3', 5'-phosphorodithioate, a second cAMP antagonist
AUTHOR(S): Botelho, Lynne H. Parker; Webster, Leland C.; Rothermel, John D.; Baraniak, Janina; Stec, Wojciech J.
CORPORATE SOURCE: Sandoz Res. Inst., Sandoz, Inc., East Hanover, NJ, 07936, USA
SOURCE: J. Biol. Chem. (1988), 263(11), 5301-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A single S substitution for either the axial or the **equatorial** exocyclic O of cAMP results in diastereomeric phosphorothioate analogs of cAMP with agonist vs. antagonist properties towards activation of **cAMP-dependent protein kinase.** S substitutions for both of the exocyclic O atoms of cAMP results in a dithioate analog of cAMP, adenosine cyclic 3',5'-phosphorodithioate (cAMPS2), which has antagonist properties. The cAMPS2 displaced [3H]cAMP from the binding sites on bovine heart type II **cAMP-dependent protein kinase** (as demonstrated by equil. dialysis expts.) with an apparent dissocn. const. (Kd) of 6.3 .mu.M. The addn. of 10, 30, or 100 .mu.M cAMP2 when measuring cAMP-induced activation of pure porcine heart type II **cAMP-dependent protein kinase** resulted in a concn.-dependent increase in the amt. of cAMP required to produce half-maximal activation (EC50). A plot of the EC50 values as a function of the cAMPs2 concn. resulted in a straight line from which a Ki value of 4 .mu.M was derived. The cAMPS2 had no significant effect on the degree of cooperativity (n) of cAMP activation of the holoenzyme. The most important structural requirement for the dissocn. of the holoenzyme is apparently an **equatorial** exocyclic O.

IT **73208-40-9**
RL: BIOL (Biological study)
(**cAMP-dependent protein kinase** inhibition by, kinetics of, diastereoisomer inhibition in relation to)
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



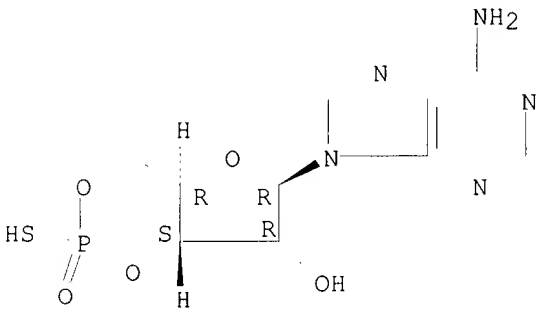
IT **23645-17-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of and **cAMP-dependent protein kinase** inhibition by)

RN 23645-17-2 HCAPLUS

CN Adenosine, cyclic 3',5'-(hydrogen phosphorothioate) (8CI, 9CI) (CA INDEX NAME)

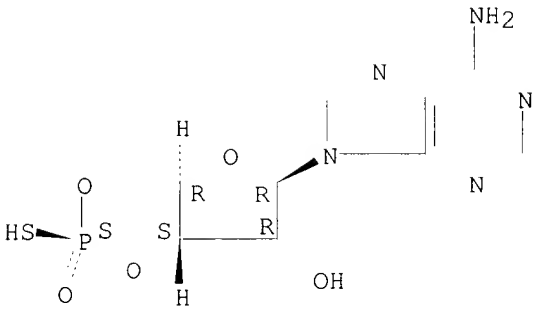
Absolute stereochemistry.



=> d ibib abs hitstr l44 6

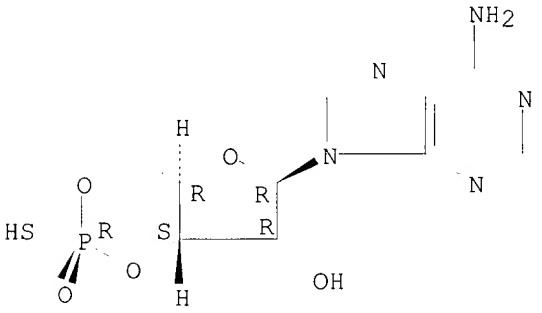
L44 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:218131 HCAPLUS
DOCUMENT NUMBER: 108:218131
TITLE: A mechanistic and kinetic analysis of the interactions of the diastereoisomers of adenosine 3',5'-(cyclic)phosphorothioate with purified **cyclic AMP-dependent protein kinase**
AUTHOR(S): Rothermel, John D.; Botelho, Lynne H. Parker
CORPORATE SOURCE: Sandoz Res. Inst., Sandoz Pharm. Corp., East Hanover, NJ, 07936, USA
SOURCE: Biochem. J. (1988), 251(3), 757-62
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding affinities of the diastereoisomers of adenosine 3',5'-(cyclic)phosphorothioate Sp-cAMP[S] and Rp-cAMP[S] for the cAMP-binding sites on purified and reconstituted pig heart type II **cAMP-dependent protein kinase** holoenzyme were detd. by measuring the ability of these compds. to displace [3H]cAMP from this enzyme. The cAMP agonist, Sp-cAMP[S], displaced 50% of the [3H]cAMP bound to the holoenzyme at a concn. 10-fold higher than that of cAMP; Rp-cAMP[S], a cAMP antagonist, required a 100-fold higher concn. relative to cAMP. The activation of the isolated holoenzyme, detd. as phosphotransferase activity, was measured in the presence of the agonist and in the absence and presence of increasing concns. of the antagonist. The results of fitting the activation data to sigmoid curves with a nonlinear-regression program and to Hill plots by using a linear-regression program showed that Rp-cAMP[S] had no effect on Vmax, increased the concn. for half-maximal activation values for agonist activation, and had no effect on the cooperativity of activation. A Ki of 11 .mu.M was detd. for Rp-cAMP[S] inhibition of cAMP-induced activation of purified type II **cAMP-dependent protein kinase**. The PAGE of the holoenzyme under nondenaturing conditions in the presence of satg. concns. of the diastereoisomers resulted in 100% dissocn. of the subunits with Sp-cAMP[S] and 0% dissocn. with Rp-cAMP[S]. Thus, the isomer with an axial exocyclic S atom, Sp-cAMP[S], binds to the holoenzyme, releases the catalytic subunit, and activates the phosphotransferase activity, whereas Rp-cAMP[S], the isomer with an **equatorial** exocyclic S atom, binds to the holoenzyme but does not result in dissocn., and acts as a competitive inhibitor of phosphotransferase activity.
IT **71774-13-5 73208-40-9**
RL: BIOL (Biological study)
(protein kinase interaction with, kinetics and mechanism of)
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

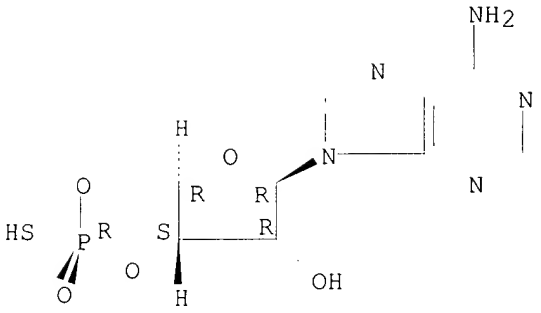
Absolute stereochemistry.



=> d ibib abs hitstr l44 7

L44 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:473955 HCAPLUS
DOCUMENT NUMBER: 107:73955
TITLE: (Rp)-cAMPS, an antagonist of cAMP in Dictyostelium discoideum
AUTHOR(S): Van Haastert, Peter J. M.; Kesbeke, Fanja; Konijn, Theo M.; Baraniak, Janina; Stec, Wojciech; Jastorff, Bernd
CORPORATE SOURCE: Zool. Lab., Univ. Leiden, Leiden, 2311 GP, Neth.
SOURCE: Bioact. Mol. (1987), 3(Biophosphates Their Analogues), 469-83
CODEN: BMOLEY
DOCUMENT TYPE: Journal
LANGUAGE: English
AB D. discoideum Cells contain a cell surface cAMP receptor that mediates the cAMP-induced activation of adenylate and guanylate cyclase. These cells also possess a surface cyclic nucleotide phosphodiesterase and an intracellular **cAMP-dependent protein kinase**. The cyclic nucleotide specificity of cAMP binding to surface receptors is quite distinct from the specificity of phosphodiesterase and protein kinase. On the other hand, the specificity of cAMP binding to surface receptors, and the cAMP-induced activation of adenylate and guanylate cyclase, are nearly identical, indicating that these responses are mediated by binding of cAMP to the surface receptor. (Rp)-cAMPs, in which the **equatorial** oxygen atom is replaced by a sulfur atom, is an exception. The chem. stability of this compd. was investigated, because the possible side-products, cAMP and (Sp)-cAMPS, are potent activators of the receptor. (Rp)-cAMPS was stable in respect to the formation of (Sp)-cAMPS. However, the analog was degraded to cAMP with a rate of 0.08%/yr when stored dry at -20.degree., and in soln. with a rate of 0.21%/yr at -20.degree., 0.1%/wk at +20.degree., and 0.35%/h at 100.degree.. The biol. properties of the highly purified compd. were investigated. (Rp)-cAMPS effectively binds to the receptor, but it is unable to induce the activation of adenylate or guanylate cyclase. Furthermore, (Rp)-cAMPS effectively blocks the cAMP-induced activation of these enzymes. Thus, (Rp)-cAMPs is an antagonist of cAMP in Dictyostelium. The compd. can be used in this organism only after extensive purifn., because cAMP impurities as little as 0.15% may render the compd. partially agonistic. The cAMP can be removed by chromatog. or, more easily, by incubation of (Rp)-cAMPS with cyclic nucleotide phosphodiesterase.
IT **73208-40-9**
RL: BIOL (Biological study)
(as cAMP antagonist, in Dictyostelium discoideum)
RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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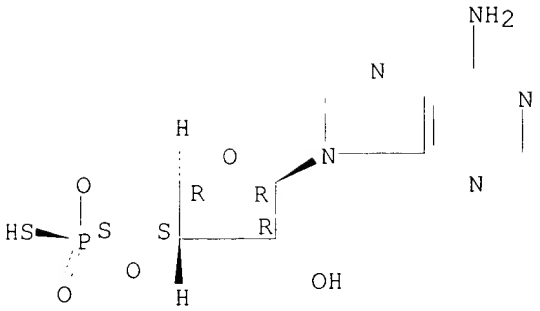
=> d ibib abs hitstr l44 8

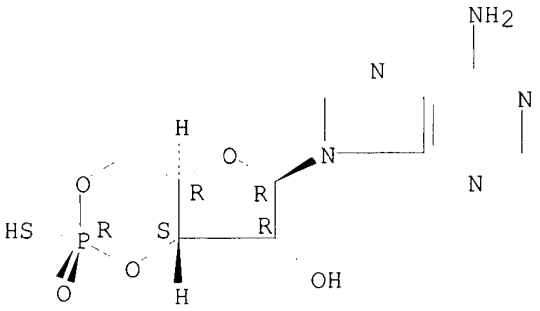
L44 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:625562 HCAPLUS
DOCUMENT NUMBER: 101:225562
TITLE: Inhibitory action of certain cyclophosphate derivatives of cAMP on **cAMP-dependent protein kinases**
AUTHOR(S): De Wit, Rene J. W.; Hekstra, Doeke; Jastorff, Bernd; Stec, Wojciech J.; Baraniak, Janina; Van Driel, Roel; Van Haastert, Peter J. M.
CORPORATE SOURCE: Zool. Lab., Univ. Leiden, Leiden, NL-2311-GB, Neth.
SOURCE: Eur. J. Biochem. (1984), 142(2), 255-60
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of cAMP derivs. with modifications in the adenine, ribose, and cyclophosphate moiety were screened for their binding affinity for the 2 types of cAMP-binding sites in mammalian protein kinase **type I**. In addn., the activation of the kinase by these analogs was monitored. The binding data indicated that cAMP is bound to both sites in a comparable manner; the adenine appears to have no H-bond interactions with the binding sites, whereas the ribose may be bound by 3 H bonds involving the 2'-, 3'-, and 5'-positions of cAMP. The binding data were not conclusive about the nature of the interaction with the exocyclic O atoms on P, although a charge interaction seemed to be absent. The cAMP mol. seemed to be bound in the syn conformation. The results of activation expts. showed that modifications in the adenine and ribose moiety do not affect the maximal activation level, whereas alteration of the 2 exocyclic O atoms may result in a reduced maximal activation level and in 1 case, (Rp)-adenosine 3',5'-monophosphorothioate [Rp-cAMPS], in total absence of activation even at concns. at which the analog sats. both binding sites. Since occupancy of the cAMP-binding sites by this deriv. apparently did not lead to activation of the enzyme, it was investigated whether this compd. could antagonize the activation by cAMP. Indeed (Rp)-cAMPS inhibited cAMP-stimulated kinase activity at concns. compatible to its binding affinity. Also, with mammalian protein kinase type II (Rp)-cAMPS showed antagonistic activity, whereas with a **cAMP-dependent protein kinase** from Dictyostelium discoideum partial agonistic activity was obsd. Previously a mechanism for activation of protein kinase **type I** was proposed involving a charge interaction between the **equatorial** exocyclic O atom and the binding site. This was based on measurements with impure prepns. of (Rp)-cAMPS and the Rp and Sp isomers of adenosine 3',5'-monophosphodimethylamidate, cAMPN(CH3)2. The present work using highly purified compds. suggested the absence of a charge interaction, since the uncharged analog (Sp)-cAMPN(CH3)2 activates the kinase effectively. The data seemed compatible with an activation model involving the formation of a covalent bond with P in both cAMP-binding sites.
IT **71774-13-5 73208-40-9**
RL: PROC (Process)
(protein kinase binding of, structure in relation to)
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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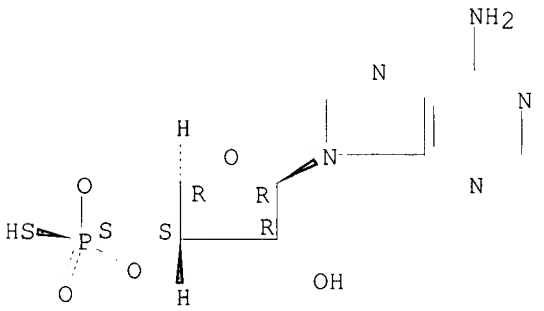
L44 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:565758 HCAPLUS
DOCUMENT NUMBER: 101:165758
TITLE: Competitive cAMP antagonists for cAMP-receptor proteins
AUTHOR(S): Van Haastert, Peter J. M.; Van Driel, Roel; Jastorff, Bernd; Baraniak, Janina; Stec, Wojciech J.; De Wit, Rene J. W.
CORPORATE SOURCE: Zool. Lab., Univ. Leiden, Leiden, 2311 GP, Neth.
SOURCE: J. Biol. Chem. (1984), 259(16), 10020-4
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 2 exocyclic O atoms at P of cAMP were replaced by a S atom or by a dimethylamino group. These substitutions introduce chirality at the P atom; therefore, 2 diastereoisomers are known for each deriv.: (SP)-cAMPS [(SP)-adenosine 3',5'-monophosphorothioate], (RP)-cAMPS, (SP)-cAMPNMe2 (SP)-adenosine 3',5'-monophosphodimethylamidate], and (RP)cAMPNMe2. The agonistic and antagonistic activities of these compds. was investigated in 4 cAMP-dependent reactions: activation of the cellular slime mold Dictyostelium discoideum via its cell surface cAMP receptor, and phosphorylation by **cAMP-dependent protein kinases type I**, type II (both mammalian enzymes), and type D (derived from D. discoideum). The compds. (SP)-cAMPS and (SP)-cAMPNMe2 are (mostly full) agonists for the 4 proteins. Half-maximal activation is at micromolar concns. (0.8-7 .mu.M). (RP)-CAMPS is a full antagonist for the cell surface receptor and protein kinases **type I** and II, with apparent inhibition consts. of 0.8-8 .mu.M. This compd. is a partial agonist for protein kinase type D, where it induces maximally 50% activation of the enzyme if compared with cAMP. (RP)-CAMPNMe2 is a full antagonist for the cell surface receptor, and for protein kinase type II. This compd. is a partial agonist for protein kinase **type I** (.gtoreq. 50% activation if compared with cAMP), and inactive for protein kinase type D. This deriv. is 25-fold less active as an antagonist than (RP)-cAMPS. The activity of mixts. of different concns. of the antagonist (RP)-cAMPS with different concns. of cAMP reveals that the compd. is a competitive antagonist of cAMP at micromolar concns.

IT **71774-13-5 73208-40-9**
RL: PROC (Process)
(cAMP receptor proteins binding of)

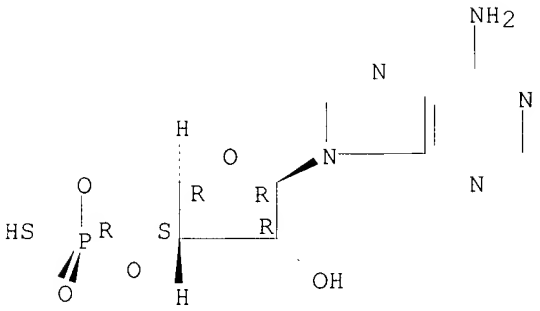
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr l44 10

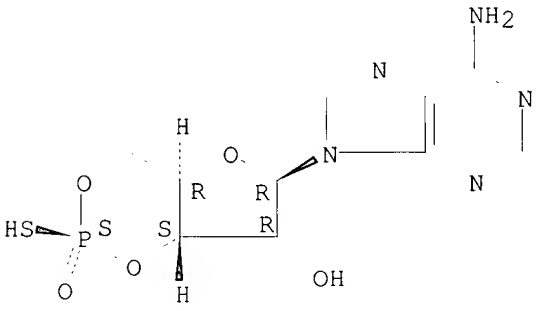
L44 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:558332 HCAPLUS
DOCUMENT NUMBER: 97:158332
TITLE: Ligand binding properties of the cytoplasmic cAMP-binding protein of Dictyostelium discoideum
AUTHOR(S): De Wit, Rene J. W.; Arents, Jos C.; Van Driel, Roel
CORPORATE SOURCE: Zool. Lab., Univ. Leiden, Leiden, 2311 GP, Neth.
SOURCE: FEBS Lett. (1982), 145(1), 150-4
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Equil. and kinetic studies of the interaction of cAMP with the 40,000-dalton cAMP-binding protein (40 K protein) of D. discoideum cytoplasm were carried out, and the binding site structure of the protein was probed with 16 cAMP analogs. At cAMP concns. .ltoreq.3 .times. 10-8 M, 40 K protein interacted with cAMP via a high-affinity binding component with a Ka of 1.3 nM. Binding was noncooperative and unaffected by ATP. At higher cAMP concns., low-affinity, ATP-inhibited binding was obsd. Analog binding studies showed the absence of adenine base interaction, but indicated that the ribose moiety forms .gtoreq.3 H bonds with the protein. It is likely that cAMP binds in the syn conformation, and the phosphate group is probably charged. Comparative studies revealed close similarities between 40 K protein and the regulatory subunit of mammalian protein kinase **type I** in cAMP interactions, thus supporting the claim that 40 K protein is the regulatory subunit of a **cAMP-dependent protein kinase** in Dictyostelium cytoplasm. Binding of cAMP by the chemotactic cAMP receptor of the D. discoideum membrane is of a completely different nature.

IT **71774-13-5 73208-40-9**
RL: BIOL (Biological study)
(cAMP-binding protein of Dictyostelium discoideum interaction with)

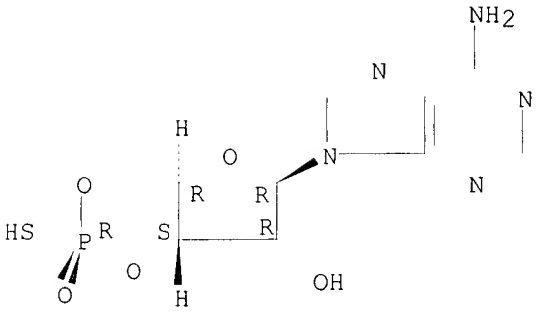
RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73208-40-9 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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=> d ibib abs hitstr l44 11

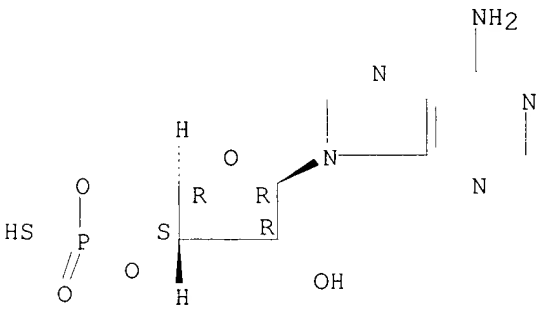
L44 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:176778 HCAPLUS
DOCUMENT NUMBER: 96:176778
TITLE: Cyclic AMP derivatives as tools for mapping cyclic AMP binding sites of **cyclic AMP-dependent protein kinases** I and II
AUTHOR(S): Miller, Jon P.
CORPORATE SOURCE: Life Sci. Div., SRI Int., Menlo Park, CA, 94025, USA
SOURCE: Adv. Cyclic Nucleotide Res. (1981), 14, 335-44
CODEN: ACNRCW; ISSN: 0084-5930
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ability of 48 cAMP analogs with structural modifications in the adenine, ribose, and cyclic phosphate moieties to activate protein kinase (PK) I from rabbit and porcine skeletal muscle and PK II from bovine brain and cardiac muscle was examd. The potency, relative to that of cAMP, of each analog as a PK I or PK II activator is expressed as a Ka' value. Each analog demonstrates comparable Ka' values with the two PK I isozymes, and likewise quite similar Ka' values with the two PK II isozymes. There are a no. of significant differences between the cAMP-binding sites on PK I and those on PK II. The 2 isozymes have clearly different binding locales adjacent to the 2-, 6-, and 8-positions of the adenine ring. PK I and PK II have differential susceptibilities to the effects of alterations in the electron distribution in the adenine ring. The 2 isozymes demonstrate significant differences in the putative binding interactions between the 2'-, 3'-, or 5'-position or the cyclic phosphate moiety and their resp. regulatory subunits. The obsd. differences between the PK I and PK II cAMP binding sites are consistent with the results of spectroscopic studies, which revealed that the cAMP binding sites of the **type I** and type II regulatory subunits differ considerably, and with the results of partial trypsin hydrolysis, which yielded different cAMP-binding fragments.

IT **23645-17-2 50721-39-6**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(protein kinases I and II activation by, structure in relation to)

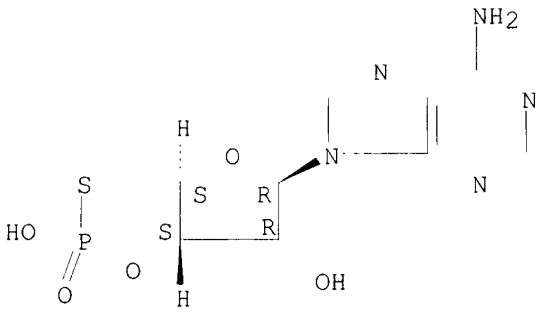
RN 23645-17-2 HCAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphorothioate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 50721-39-6 HCAPLUS
CN Adenosine, 5'-thio-, cyclic 3',5'-(hydrogen phosphate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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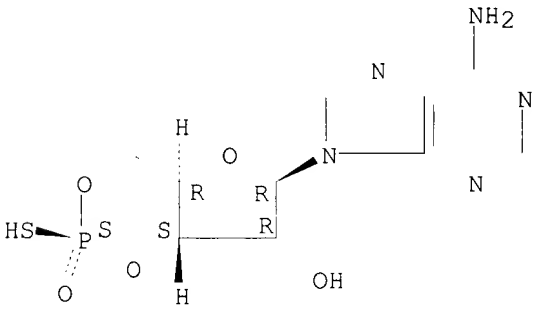
L44 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:138834 HCAPLUS
DOCUMENT NUMBER: 96:138834
TITLE: Interaction of cAMP derivatives with the 'stable' cAMP-binding site in the **cAMP-dependent protein kinase type I**
AUTHOR(S): De Wit, Rene J. W.; Hoppe, Juergen; Stec, Wojciech J.; Baraniak, Janina; Jastorff, Bernd
CORPORATE SOURCE: Fachber. Biol./Chem., Univ. Bremen, Bremen, D-2800/33, Fed. Rep. Ger.
SOURCE: Eur. J. Biochem. (1982), 122(1), 95-9
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Binding of cAMP to the stable cAMP-binding sites in the regulatory subunit of **cAMP-dependent protein kinase type I** was investigated using a set of 18 selected derivs. All the tested analogs were competitive with [3H]cAMP and Ki values from 12 nM to 20 .mu.M with the free regulatory subunit were detd. The cAMP mol. appeared to be bound by 3 specific H-bonds to the 5'- and 3'-O, the 2'-hydroxyl, and an ion pair interaction between the neg. charge in **equatorial** position and a pos. charged amino acid side chain. The adenine base was rather unspecifically bound with no H-bonds involved. This binding specificity of the stable site was similar to the requirement for dissocn. as detd. by the activation of the kinase by a resp. analog. This indicated that occupation of the stable sites led to activation of the protein kinase. The presence of the catalytic subunit reduced the affinity of most analogs. The binding of one deriv. with the neg. charge fixed in the axial position was not influenced by the addn. of the catalytic subunit and ATP. A plausible model for a conformational change during the activation process in the stable site was discussed.

IT **71774-13-5 73208-40-9**
RL: BIOL (Biological study)
(protein kinase of muscle binding of, kinetics of)

RN 71774-13-5 HCAPLUS
CN Adenosine, cyclic 3',5'-[hydrogen (S)-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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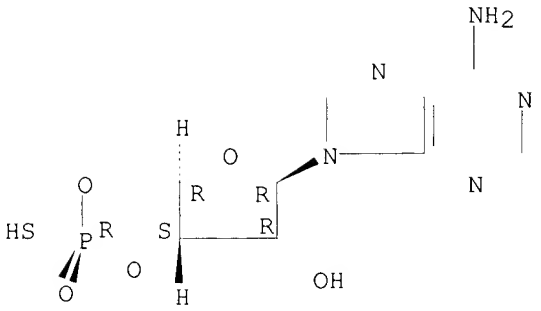
CN Adenosine, cyclic 3',5'-[hydrogen [P(R)]-phosphorothioate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.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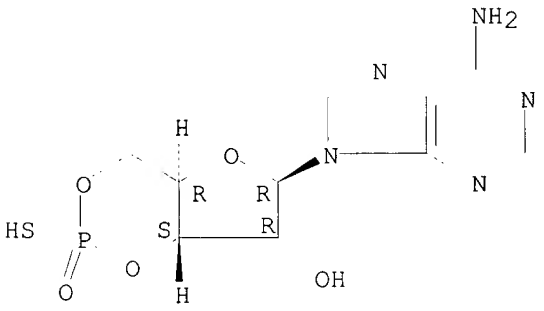
L44 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:116796 HCAPLUS
DOCUMENT NUMBER: 94:116796
TITLE: Mapping adenosine cyclic 3',5'-phosphate binding sites on **type I** and type II adenosine cyclic 3',5'-phosphate dependent protein kinases using ribose ring and cyclic phosphate ring analogs of adenosine cyclic 3',5'-phosphate
AUTHOR(S): Yagura, Terry S.; Miller, Jon P.
CORPORATE SOURCE: Life Sci. Div., SRI Int., Menlo Park, CA, 94025, USA
SOURCE: Biochemistry (1981), 20(4), 879-87
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of cAMP derivs. contg. modifications or substitutions in either the 2'-, 3'-, 4'-, or 5'-position or the phosphate were examd. for their abilities to activate **type I** isoenzymes of **cAMP-dependent protein kinase** (PK I) from rabbit or porcine skeletal muscle and type II isoenzymes of **cAMP-dependent protein kinase** (PK II) from bovine brain and heart. The studies revealed that the activation of both PK I and PK II isoenzymes requires a 2'-hydroxyl group in the ribo configuration, a 3'-O atom in the ribo configuration, and a charged cyclic phosphate. The 2 isoenzymes appeared to differ in those portions of their resp. cAMP-binding sites that are adjacent to the 4'-position of the ribose ring and the 3'-position, 5'-position, and phosphate portion of the cyclic phosphate ring.
IT **23645-17-2 50721-39-6**
RL: BIOL (Biological study)
(protein kinase isoenzyme specificity for)
RN 23645-17-2 HCAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphorothioate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 50721-39-6 HCAPLUS
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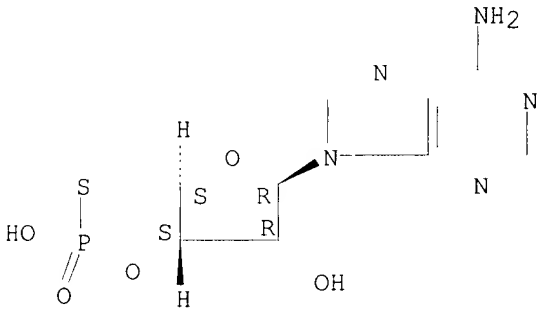
Absolute stereochemistry.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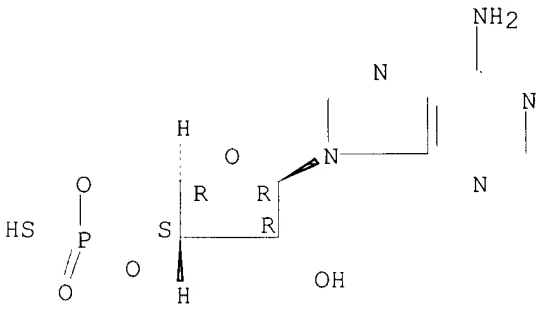
=> d ibib abs hitstr l44 14

L44 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:106362 HCAPLUS
DOCUMENT NUMBER: 92:106362
TITLE: A model for the chemical interactions of adenosine 3':5'-monophosphate with the R subunit of protein kinase **type I**. Refinement of the cyclic phosphate binding moiety of protein kinase **type I**
AUTHOR(S): Jastorff, Bernd; Hoppe, Juergen; Morr, Michael
CORPORATE SOURCE: Fachber. Biol. Chem., Univ. Bremen, Bremen, Fed. Rep. Ger.
SOURCE: Eur. J. Biochem. (1979), 101(2), 555-61
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cAMP receptor site in the regulatory subunit of **cAMP-dependent protein kinase type I** was mapped using analogs of cAmP in which the ribose phosphate moiety was systematically modified. Electronic alteration of the cyclophosphate ring at the 3' and 5' positions by S and N decreased the affinity of these analogs toward the kinase. Substituents at these positions are not tolerated. In testing the sepd. diastereomers of derivs. in which 1 of the exocyclic atoms at the P atom was substituted by S, it was found that 1 diastereoisomer was preferentially recognized. Thus, it is proposed that the hydrophilic cyclic phosphate-ribose moiety of cAMP is bound to the kinase via its 3'- and 5'-O atoms, the 2'-hydroxyl group, and the neg. charge in a fixed position. Probably, the adenine moiety is bound in a hydrophobic cleft without any H-bond interactions. The chem. interactions between cAMP and the R subunit of protein kinase **type I** differed from those found for the binding of cAMP to the chemoreceptor of Dictyostelium discoideum.
IT **23645-17-2**
RL: PROC (Process)
(protein kinase regulatory subunit binding of)
RN 23645-17-2 HCAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphorothioate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



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File 410:Chronolog(R)  1981-2002/Jul
       (c) 2002 The Dialog Corporation

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removal, customized scheduling. See HELP ALERT.

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11254815   21291555   PMID: 11398815
   Tsl  and  LP-BM5: a comparison of two murine retrovirus models for
HIV.
  Clark S; Duggan J; Chakraborty J
  Department of Physiology and Molecular Medicine, Medical College of Ohio,
Toledo 43614-5804, USA.
  Viral  immunology (United  States)  Jun  2001,  14  (2)  p95-109,  ISSN
0882-8245   Journal Code: 8801552
  Document type: Journal Article; Review; Review, Tutorial
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The  ts1  murine  leukemia virus produces an immunodeficiency
 state  in  mice  that  parallels  human immunodeficiency virus (HIV)
infection  in  humans.  Other murine leukemia viruses, such as LP-BM5
used  in  the  murine  acquired  immune  deficiency  virus  (
MAIDS )  model, have been studied extensively as a small animal model
for HIV research, but lack many key similarities to HIV. Mice infected with
ts1, however, utilize CD4 target cells for infection, undergo neuronal loss
and  demyelination,  and  develop  clinical  immunodeficiency . These
features  make  this retrovirus in many ways an ideal candidate for a small
animal  model  for  HIV  research.  In this review article, the early
development, the molecular and clinical pathogenesis of both the ts1 mutant
of  the  Moloney murine leukemia virus and LP-BM5 are examined. Based
on  an  extensive  evaluation  of  the  literature on LP-BM5 and ts1, it is
concluded  that  the  ts1 virus may serve as a better animal model to human
retrovirus infection.


 6/3,AB/2     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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09814100   BIOSIS NO.: 199598269018
Cytomegalovirus retinitis during AIDS: Current issues and future
  directions.
AUTHOR: Dix Richard D(a); Cray Carolyn; Cousins Scott
AUTHOR ADDRESS: (a)Dep. Ophthalmol., Bascom Palmer Eye Inst., Univ. Miami
  Sch. Med., Miami, FL 33101**USA
JOURNAL: Regional Immunology  6 (1-2):p112-118
ISSN: 0896-0623
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytomegalovirus (CMV) retinitis is the leading cause of blindness
  in patients with acquired immune deficiency syndrome (AIDS).
  Before improved therapeutic approaches can be developed to manage this
  devastating sight-threatening disease, specific questions pertinent to
  the pathophysiology of CMV retinitis must be addressed. These questions
  relate to the origin of virus responsible for retinitis, spread of virus
  within the retina, the immunopathogenesis of retinal destruction, and the
  fate of virus during traditional antiviral therapy. In this review,
  we examine for each question the clinical rationale, the experimental
  data, and the clinical implications associated with these data. In
  particular, two experimental systems are emphasized. One is an in vitro
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system to study the susceptibility of human retinal pigment epithelium to CMV infection. The other involves clinically-relevant **murine** models of CMV retinitis, especially one of retrovirus-induced **immunodeficiency** (**MAIDS**). We suggest that immune-based therapy alone or in combination with traditional chemotherapy offers improved prospects for maintaining subclinical CMV infection in the immunosuppressed individual, thereby preventing CMV retinitis.

6/3,AB/3 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08341318 BIOSIS NO.: 000043073441
RETROVIRUS-INDUCED **IMMUNODEFICIENCY** IN THE **MOUSE MAIDS** AS A MODEL FOR AIDS
AUTHOR: MORSE H C III; CHATTOPADHYAY S K; MAKINO M; FREDRICKSON T N; HUGIN A W; HARTLEY J W
AUTHOR ADDRESS: BUILD. 7, ROOM 304, NATL. INST. HEALTH, BETHESDA, MD. 20892.
JOURNAL: AIDS (PHILA) 6 (7). 1992. 607-621. 1992
CODEN: AIDSE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1992

6/3,AB/4 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07758547 BIOSIS NO.: 000041056798
MURINE ACQUIRED IMMUNODEFICIENCY SYNDROME **MAIDS** AN ANIMAL MODEL TO STUDY THE AIDS PATHOGENESIS
AUTHOR: JOLICOEUR P
AUTHOR ADDRESS: LAB. MOL. BIOL., CLINICAL RES. INST. MONTREAL, 110 PINE AVE. W., MONTREAL, QUEBEC, CAN. H2W 1R7.
JOURNAL: FASEB (FED AM SOC EXP BIOL) J 5 (10). 1991. 2398-2405. 1991
FULL JOURNAL NAME: FASEB (Federation of American Societies for Experimental Biology) Journal
CODEN: FAJOE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1991

6/3,AB/5 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06834529 BIOSIS NO.: 000038006753
PATHOGENESIS OF **MAIDS** A RETROVIRUS-INDUCED **IMMUNODEFICIENCY** DISEASE OF MICE
AUTHOR: CHATTOPADHYAY S K; MAKINO M; HARTLEY J W; MORSE H C III
AUTHOR ADDRESS: LAB. IMMUNOPATHOL., NATL. INST. ALLERGY AND INFECTIOUS DISEASES, NATL. INST. HEALTH, BUILD. 7, ROOM 302, BETHESDA, MD. 20892, USA.
JOURNAL: WU, B.-Q. AND J. ZHENG (ED.). IMMUNE-DEFICIENT ANIMALS IN EXPERIMENTAL MEDICINE; 6TH INTERNATIONAL WORKSHOP, BEIJING, CHINA, JULY 3-6, 1988. XIV+361P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, NEW YORK, USA. ILLUS. ISBN 3-8055-4934-2. 0 (0). 1989. 12-18. 1989
CODEN: 28286

DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1989
? t s7/3,ab/all

7/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13504651 22092263 PMID: 12097374
Induction of CD4 T cell changes in **murine** AIDS is dependent on costimulation and involves a dysregulation of homeostasis.
Yen Michael H; Lepak Nancy; Swain Susan L
Department of Biology, University of California at San Diego, La Jolla, CA 92093, USA.
Journal of immunology (Baltimore, Md. : 1950) (United States) Jul 15 **2002**, 169 (2) p722-31, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI21225; AI; NIAID; AI26887; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Strong CD4 T cell activation and proliferation are seen in susceptible mice infected with the **murine** retroviral inoculum, LP-BM5, which produces an **immunodeficiency syndrome** called **murine** AIDS (**MAIDS**). We developed a short term adoptive transfer model of **MAIDS** to examine the requirements for the CD4 T cell response. Naive CD4 T cells from uninfected donors responded quickly after adoptive transfer into **MAIDS** -infected hosts, becoming activated and proliferating within several days. Using blocking mAbs to costimulatory ligands and CD4 T cells deficient in expression of their receptors, we found that the CD4 T cell response requires CD28:B7.1/B7.2 interactions, but not CTLA4 or CD40-CD40 ligand interactions. Naive CD4 T cells did not respond in H-2M-deficient mice with **MAIDS**, suggesting that disease requires recognition of self peptide-MHC complexes. The self MHC-dependent division and accumulation of large numbers of CD4 T cells suggest that **MAIDS** involves a disruption of the balance of homeostatic signals. Supporting this hypothesis, CD4 T cells from mice with **MAIDS** failed to regulate the homeostatic division of naive CD4 T cells in a cotransfer model. Thus, a combination of up-regulation of costimulatory ligands and disruption of homeostatic control may be responsible for CD4 lymphoproliferation in **MAIDS**.

7/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13500981 22115019 PMID: 12119508
Murine AIDS induces viremia and functional and phenotypic alterations in blood cells.
Hugin Ambros W; Wirth Susanne
Department of Dermatology, University Hospital, Geneva, Switzerland. ambros.hugin@hcuge.ch
International archives of allergy and immunology (Switzerland) Jul **2002**, 128 (3) p244-52, ISSN 1018-2438 Journal Code: 9211652
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: **Murine acquired immunodeficiency syndrome** (**MAIDS**) is characterized by generalized lymphoproliferation and progressive **immunodeficiency**. It is induced by a mixture of two replication-competent **murine** leukemia viruses (MuLV) and a disease-causing, replication-incompetent defective MuLV.

Infection leads to specific phenotypic and functional alterations of lymphocytes in lymphoid organs. METHODS: We analyzed phenotypic, virological and functional parameters in the blood of mice infected with **MAIDS** virus. RESULTS: Disease progression correlated with increasing viremia, a loss of mitogen responsiveness of T lymphocytes, and the appearance of CD4+ Thy1- T lymphocytes. At >9 weeks after infection, the distribution of leukocyte cell populations became very heterogeneous, and late-stage leukemic events were observed in 5 of 23 mice. CONCLUSIONS: Virus titers, mitogen responsiveness and the presence of CD4+ Thy1- T lymphocytes can efficiently be monitored in the blood and serve as diagnostic parameters to monitor disease progression. Acute leukemic events occurring at the terminal stage could be responsible for the death of at least some of the mice with **MAIDS**. Copyright 2002 S. Karger AG, Basel

7/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13262776 21906538 PMID: 11908922
Chemical sympathectomy has no effect on the severity of **murine** AIDS: **murine** AIDS alone depletes norepinephrine levels in infected spleen.

Kelley Sheila P; Moynihan Jan A; Stevens Suzanne Y; Grota Lee J; Felten David L
Center for Psychoneuroimmunology Research, University of Rochester Medical Center, 300 Crittenden Boulevard, Rochester, New York 14642, USA.

Brain, behavior, and immunity (United States) Apr **2002**, 16 (2) p118-39, ISSN 0889-1591 Journal Code: 8800478
Contract/Grant No.: R37 MH42076; MH; NIMH
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Numerous studies have shown that alterations in sympathetic nervous system (SNS) function produced by beta-adrenergic receptor blockade or chemical sympathectomy can produce changes in T and B lymphocyte function and both innate and **acquired** immune responses. However, fewer studies have investigated changes in immune response following SNS alterations in animal models of disease. We tested whether blocking SNS activity using 6-OHDA or the beta-receptor antagonist nadolol alters the typical pattern in production of T helper 1 (Th1) and Th2 cytokines seen in cultures of spleen cells from C57BL/6 mice infected with **murine** AIDS (**MAIDS**). We found that neither method of sympathetic blockade affected cytokine response to **MAIDS**. We also found that the norepinephrine concentration and content of the spleen were reduced dramatically by the **MAIDS** infection itself at 3 and 6 weeks after LP-BM5 inoculation. This finding has not been previously reported in mice with **MAIDS** and suggests that the viral infection itself produces a functional sympathectomy in the spleen, a target of that infection. Copyright 2001 Elsevier Science (USA).

7/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13249950 21968753 PMID: 11971678
Induction of **murine** AIDS virus-related sequences after burn injury.

Cho Kiho; Adamson Lee K; Greenhalgh David G
Burn Surgery, Shriners Hospitals for Children Northern California, Sacramento, California 95817, USA.

Journal of surgical research (United States) May 1 **2002**, 104 (1) p53-62, ISSN 0022-4804 Journal Code: 0376340
Contract/Grant No.: R01-GM50959; GM; NIGMS
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

To better understand the molecular signaling events leading to systemic inflammatory response **syndrome** (SIRS) and multiple organ failure (MOF), changes in gene expression profiles after burn injury were investigated by differential display. C57BLKS/J mice were subjected to 18% total body surface area (TBSA) full-thickness burn and various tissues were harvested at multiple time points after injury. Initial differential display revealed that retroviral transcripts similar to the envelope sequence of **murine** AIDS (**MAIDS**) virus were rapidly and transiently up-regulated after injury. Subsequent RT-PCR and DNA sequencing analyses confirmed the transient up-regulation of retroviral sequences similar to those of the **MAIDS** virus. In addition, the presence and induction of the subgenomic envelope transcripts of these **MAIDS** virus-related sequences, including a novel double spliced message, were identified after burn injury. These data suggest that the transcriptional efficiency of the integrated retroviral DNA and reactivation of defective **MAIDS** virus-related sequences may be affected by pathophysiological signals, such as burn injury. The elevated expression of these **MAIDS** virus-related retroviral sequences may affect the transcriptional activities of the flanking genes at the integration sites and may be a cause of altered local and systemic immune responses to burn-related stress.

7/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11248973 21280886 PMID: 11387259

Increased cAMP levels and protein kinase (PKA) type I activation in CD4+ T cells and B cells contribute to retrovirus-induced **immunodeficiency** of mice (**MAIDS**): a useful in vivo model for drug testing.

Rahmouni S; Aandahl E M; Trebak M; Boniver J; Tasken K; Moutschen M
Department of Pathology, University of Liege, Liege, Belgium.

FASEB journal : official publication of the Federation of American Societies for Experimental Biology (United States) Jun **2001**, 15 (8) p1466-8, ISSN 0892-6638 Journal Code: 8804484
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11216983 21240665 PMID: 11342621

B cell **immunodeficiency** fails to develop in CD4-deficient mice infected with BM5: **murine** AIDS as a multistep disease.

Harris D P; Koch S; Mullen L M; Swain S L
The Trudeau Institute, Saranac Lake, NY 12983, USA.

Journal of immunology (Baltimore, Md. : 1950) (United States) May 15 **2001**, 166 (10) p6041-9, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: CA56290; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The **immunodeficiency syndrome murine** AIDS (**MAIDS**), caused by the BM5 retrovirus preparation, involves the activation, division, and subsequent anergy of the entire CD4(+) T cell population as well as extensive B cell hyperproliferation and hypergammaglobulinemia, resulting in splenomegaly and lymphadenopathy, followed many weeks later by

death. The development of **MAIDS** requires CD4(+) T cells and MHC class II expression by the infected host, supporting a role for T-B interaction in disease development or progression. To explore this possibility, we examined development of **MAIDS** in mice deficient in CD4 (CD4 knockout), in which T-B interactions are compromised. We find that in CD4 knockout hosts, BM5 causes T cell **immunodeficiency** in the remaining T cells but has only a limited ability to induce B cell phenotypic changes, hyperproliferation, hypergammaglobulinemia, or splenomegaly. There is also delayed death of infected mice. This implies that CD4 dependent T-B interaction is needed to induce the B cell aspects of disease and supports a multistep mechanism of disease in which B cell changes follow and are caused by CD4(+) T cell effects.

7/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11152587 21165268 PMID: 11264347
Characterization of the CD154-positive and CD40-positive cellular subsets required for pathogenesis in retrovirus-induced **murine immunodeficiency**.
Green K A; Noelle R J; Durell B G; Green W R
Department of Microbiology and Immunology, Dartmouth Medical School and Norris Cotton Cancer Center, Lebanon, New Hampshire 03756, USA.
Journal of virology (United States) Apr **2001**, 75 (8) p3581-9, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: CA23108; CA; NCI; CA50157; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Genetically susceptible C57BL/6 (B6) mice that are infected with the LP-BM5 isolate of **murine** retroviruses develop profound splenomegaly, lymphadenopathy, hypergammaglobulinemia, terminal B-cell lymphomas, and an **immunodeficiency** state bearing many similarities to the pathologies seen in AIDS. Because of these similarities, this **syndrome** has been called **murine** AIDS (**MAIDS**). We have previously shown that CD154 (CD40 ligand)-CD40 molecular interactions are required both for the initiation and progression of **MAIDS** . Thus, in vivo anti-CD154 monoclonal antibody (MAb) treatment inhibited **MAIDS** symptoms in LP-BM5-infected wild-type mice when either a short course of anti-CD154 MAb treatment was started on the day of infection or a course was initiated 3 to 4 weeks after LP-BM5 administration, after disease was established. Here, we further characterize this required CD154-CD40 interaction by a series of adoptive transfer experiments designed to elucidate which cellular subsets must express CD154 or CD40 for LP-BM5 to induce **MAIDS**. Specifically with regard to CD154 expression, **MAIDS** -insusceptible B6 nude mice reconstituted with highly purified CD4+ T cells from wild-type, but not from CD154 knockout, B6 donors displayed clear **MAIDS** after LP-BM5 infection. In contrast, nude B6 recipients that received CD8+ T cells from wild-type B6 donors did not develop **MAIDS** after LP-BM5 infection. B6 CD40 knockout mice, which are also relatively resistant to LP-BM5-induced **MAIDS** , became susceptible to LP-BM5-induced disease after reconstitution with highly purified wild-type B cells but not after receiving purified wild-type dendritic cells (DC) or a combined CD40+ population composed of DC and macrophages obtained from B6 SCID **mouse** donors. Based on these and other experiments, we thus conclude that the cellular basis for the requirement for CD154-CD40 interactions for **MAIDS** induction and progression can be accounted for by CD154 expression on CD4+ T cells and CD40 expression on B cells.

7/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11054766 21039708 PMID: 11200058
Impaired IL-15 production associated with susceptibility of **murine** AIDS to mycobacterial infection.
Umemura M; Hirose K; Wajjwaiku W; Nishimura H; Matsuguchi T; Gotoh Y; Takahashi M; Makino M; Yoshikai Y
Laboratory of Host Defense, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Japan.
Journal of leukocyte biology (United States) Jan **2001**, 69 (1) p138-48, ISSN 0741-5400 Journal Code: 8405628
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
LP-BM5 **murine** leukemia virus (MuLV) injection causes **murine** AIDS (**MAIDS**), a disease characterized by many functional abnormalities of immunocompetent cells. We show that **MAIDS** mice are susceptible to Mycobacterium bovis Bacille Calmette-Guerin (BCG) infection as assessed by survival rate and bacterial counts. The peritoneal exudate macrophages from **MAIDS** mice produced a significant level of interleukin (IL)-12 soon after inoculation with BCG, whereas IL-15 and tumor necrosis factor (TNF) production were severely impaired in BCG-infected **MAIDS** mice. The appearance of natural killer (NK) and CD4+ T helper type 1 (Th1) cells specific for mycobacterial antigen were depressed in **MAIDS** mice after BCG infection. Thus, it appeared that impaired production of IL-15, besides other inflammatory cytokines, in **MAIDS** mice may be involved in the poor responses of the NK and Th1 cells, resulting in an increased susceptibility to BCG.

7/3,AB/9 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13741652 BIOSIS NO.: 200200370473
An analysis of the CD80/86 molecular interaction and TRAF signaling in LP-BM5 induced **murine immunodeficiency** (**MAIDS**).
AUTHOR: Green Kathy A(a); Noelle Randolph J; Sharpe Arlene H; Green William R
AUTHOR ADDRESS: (a)Microbiology, Dartmouth Medical School, 1 Medical Center Drive, Lebanon, NH, 03756**USA
JOURNAL: FASEB Journal 16 (5):pA1042 March 22, **2002**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: C57BL/6 (B6) mice, infected with the LP-BM5 isolate of **murine** retroviruses, develop splenomegaly, lymphadenopathy, hypergammaglobulinemia, terminal B cell lymphomas and an **immunodeficiency** state bearing many similarities to the pathologies seen in AIDS, hence has been referred to as **murine** AIDS or **MAIDS**. We have shown that CD154 (CD40L)/CD40 molecular interactions are required both for the initiation and progression of **MAIDS**. We also found that **MAIDS** - insusceptible B6-nude mice reconstituted with CD4+ T cells from w.t., but not from CD154 knockout (k.o) donors and B6/CD40 k.o. mice only after reconstitution with w.t., CD40+ B cells as a source for CD40 expression, became susceptible to LP-BM5 induced **MAIDS**. Recent experiments have shown that B6/CD80/CD86 (B7-1/B7-2) double k.o. mice are susceptible to LP-BM5 induced **MAIDS** pathogenesis. At 11 weeks post LP-BM5 infection, B6/CD80/86 k.o. mice had developed hypergammaglobulinemia and splenomegaly and they were

immunodeficient. Spleen cells from these mice were unable to respond normally to LPS and Con A stimulation and were impaired in their ability to generate an allo CTL response. These observations suggest that the requirement for CD154/CD40 molecular interactions for **MAIDS** disease progression are not explained simply by the well-known upregulation of CD80/86 following signling through CD40. By using TRAF transggenic mice, we are currently addessing the role of TRAF in LP-BM5 induced **MAIDS** pathogenesis.

2002

7/3,AB/10 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13741644 BIOSIS NO.: 200200370465
Elevated oxidative stress in mice infected with **murine** retrovirus and the effect of moderate Mg-deficiency.
AUTHOR: Mak I Tong(a); Basile Anthony S; Weglicki William B(a)
AUTHOR ADDRESS: (a)Physiology and Experimental Medicine, George Washington University Medical Center, 2300 Eye Street, NW, Washington, DC, 20037** USA
JOURNAL: FASEB Journal 16 (5):pA1041 March 22, **2002**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Abnormalities in cellular and circulating GSH homeostasis may play an important role in manifestations of HIV-1 infection. In this study, C57BL/6 mice (n=12) were infected by LP-BM5 **murine** leukemia virus to generate a **murine** AIDS (**MAIDS**) model analogous to human HIV-1 infection. At 12 weeks post-inoculation, total GSH in the blood samples of **MAIDS** mice decreased to varying degrees (up to 55%, mean=27% loss, $p<0.01$). Concomitantly, the antioxidant capacity of the plasma of the **MAIDS** mice decreased by 43% ($p<0.025$). Significant decreases (22-24%, $p<0.05$) in GSH were also observed in the striatum and cortex of **MAIDS mouse** brain. In separate experiments (n=4-6/group), the effect of moderate Mg-deficiency (40% Mg of normal diet) on the **MAIDS** circulating thiol status was examined. At 7 weeks, decreases in the blood GSH (apprx24%) were evident in the **MAIDS** mice. At 14 weeks, viral infection alone caused a 38% decrease ($p<0.05$) in blood GSH; however, Mg-deficiency plus virus induced a 48% GSH loss ($p<0.01$). The Mg-deficient diet alone induced a 26% ($p<0.05$) decrease in GSH. Significant protein-SH loss (39%, $p<0.05$) was also found in blood samples with combined Mg-deficiency/Infection. Because Mg-wasting may co-exist with HIV infection, the results support the hypothesis that increased oxidative stress resulting in depleted GSH may be a critical component during AIDS pathogenesis and that even moderate Mg-deficiency further aggravates the stress.

2002

7/3,AB/11 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13593435 BIOSIS NO.: 200200222256
Kinetic analysis of cytokine expression in autoimmune-like pancreatitis in **MAIDS** mice.

AUTHOR: Watanabe Shiro(a); Suzuki Kenji(a); Suriki Hidehisa(a); Yoneyama Hiroyuki(a); Baba Yasuyuki(a); Aiba Tsuneo(a); Sasaki Shunya(a); Kawauchi Yusuke(a); Kawachi Hiroshi(a); Shimizu Fujio(a); Asakura Hitoshi(a)
AUTHOR ADDRESS: (a)Niigata Univ Sch of Medicine, Niigata**Japan
JOURNAL: Gastroenterology 120 (5 Supplement 1):pA720 April, **2001**
MEDIUM: print
CONFERENCE/MEETING: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
2001

7/3,AB/12 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13464335 BIOSIS NO.: 200200093156
Pathogenesis of defective retroviruses.
BOOK TITLE: Developments in Biologicals Evolving scientific and regulatory perspectives on cell substrates for vaccine development
AUTHOR: Jolicoeur P(a)
BOOK AUTHOR/EDITOR: Brown Fred; Lewis Andrew Jr ; Peden Keith; Krause Philip: Eds
AUTHOR ADDRESS: (a)Clinical Research Institute of Montreal, 110 Pine Avenue West, Montreal, PQ, H2W 1R7**Canada
JOURNAL: Developments in Biologicals (106):p201-210 **2001**
MEDIUM: print
BOOK PUBLISHER: S. Karger Publishers Inc., 79 Fifth Avenue, New York, NY, 10003, USA
S. Karger AG, CH-4009, Basel, Switzerland
CONFERENCE/MEETING: Evolution of Cell Substrates Used in the Manufacture of Biologicals Workshop Rockville, MD, USA September 07-10, 1999
ISSN: 1424-6074 ISBN: 3-8055-7286-7 (paper)
RECORD TYPE: Citation
LANGUAGE: English
2001

7/3,AB/13 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13303392 BIOSIS NO.: 200100510541
Novel ribonucleotide reductase inhibitors, Didox and Trimidox, compared to hydroxyurea to reverse established retroviral disease in the **murine** AIDS (**MAIDS**) model.
AUTHOR: Mayhew C(a); Inayat M(a); Sumptner R; Gallicchio V; Kunder S; Wood O; Neilson C; Ussery M; Elford H
AUTHOR ADDRESS: (a)University of Wolverhampton, Wolverhampton**UK
JOURNAL: Antiviral Research 51 (1):p54 July, **2001**
MEDIUM: print
CONFERENCE/MEETING: HIV DART 2000: Frontiers in Drug Development for Antiretrovial Therapies Carolina, Puerto Rico December 17-21, 2000
ISSN: 0166-3542
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

7/3,AB/14 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

13071628 BIOSIS NO.: 200100278777
MCMV retinitis during **MAIDS** correlates with elevated levels of interleukin-4 within MCMV-infected eyes.
AUTHOR: Dix R D(a); Ekworomadu C O(a); Cousins S W
AUTHOR ADDRESS: (a)Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, AR**USA
JOURNAL: IOVS 42 (4):pS46 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

7/3,AB/15 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13060640 BIOSIS NO.: 200100267789
The effects of **murine** retroviral infection of neutrophil activation during chronic alcohol consumption.
AUTHOR: Chen Yinhong(a); Mendoza Sam; Davis-Gorman Grace; Cohen Zoe; Tuttle Hillary; Gonzales Raoul; McDonagh Paul F; Watson Ronald R(a)
AUTHOR ADDRESS: (a)The Arizona Prevention Center, University of Arizona, Tucson, AZ, 85724**USA
JOURNAL: FASEB Journal 15 (4):pA679 March 7, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The role of the acute inflammatory responses in the etiology of organ injury in AIDS is not clear, nor is the combined effects of AIDS and alcohol consumption on the inflammatory response. The aim of this study was to determine whether or not neutrophilis (PMNs) play a role in the acute inflammatory response in **Murine** AIDS (**MAIDS**) especially during chronic alcohol consumption. Four groups were studied: Control, **MAIDS**, Alcohol and Alcohol plus **MAIDS**. We induced **MAIDS** by infection with retrovirus complex LP-BM5. Ethanol (30%) was added to the drinking water for the alcohol consumption group. PMN activation was assessed by the expression of CD11b and oxygen free radical (ROS) production using flow cytometry. We found that CD11b expression was up-regulated ($p<0.05$) along with a significant increase in ROS ($p<0.001$) one month after retrovirus infection. After two months, PMN CD11b and ROS decreased. However, after three months, the infected mice demonstrated a general malaise. The expression of PMN CD11b expression ($p<0.01$) increased to a new level along with increased ROS, perhaps due to a secondary infection. These findings suggest that retrovirus initially activates PMNs, but subsequently impairs their function. In the alcohol consumption group, PMN CD11b expression was down-regulated after two months ($p<0.05$), but ROS production increased after three months ($p<0.05$). For the **MAIDS** plus Alcohol group, there were significant increases in both ROS ($p<0.001$) and CD11b expression ($p<0.01$) during the three month observation period. These results suggest that **MAIDS**

plus alcohol have a synergistic effect on PMN activation.

2001

7/3,AB/16 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13055361 BIOSIS NO.: 200100262510
Novel ribonucleotide reductase inhibitors, Didox and Trimidox, compared to hydroxyurea to reverse established disease in the **murine** AIDS (**MAIDS**) model.
AUTHOR: Elford H; Mayhew C(a); Inayat M(a); Sumptner R; Gallicchio V
AUTHOR ADDRESS: (a)U. of Wolverhampton, Wolverhampton**UK
JOURNAL: Antiviral Research 50 (1):pA57 April, **2001**
MEDIUM: print
CONFERENCE/MEETING: Fourteenth International Conference on Antiviral Research Seattle, Washington, USA April 08-12, 2001
ISSN: 0166-3542
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

7/3,AB/17 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13048540 BIOSIS NO.: 200100255689
Mouse AIDS increases coronary microvascular permeability to macromolecules.
AUTHOR: Chen Yinhong(a); Davis-Gorman Grace; Watson Ronald R(a); McDonagh Paul F
AUTHOR ADDRESS: (a)The Arizona Prevention Center, University of Arizona, Tucson, AZ, 85724**USA
JOURNAL: FASEB Journal 15 (4):pA121 March 7, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Several studies report that retrovirus impairs the blood-brain barrier. We hypothesized that the retrovirus model of AIDS in mice would increase coronary microvascular permeability to macromolecules. Coronary microvascular permeability was determined by the transcoronary leakage of fluorescent albumin (FITC-BSA). After three months of LP-BM5 Retrovirus infection, **mouse** hearts were prepared for direct visualization and quantification of transcoronary macromolecular leakage. Hearts from Control and **MAIDS** mice were isolated and perfused with diluted rat blood containing FITC-BSA. Coronary microvascular fields were observed using intravital fluorescence microscopy after 5, 15, and 25 minutes of perfusion. The videotaped results were analyzed using Dazzle DVC and Adobe software. The O/I ratio was used to quantify FITC-BSA leakage (McDonagh et al, 1983). We found that the mean O/I ratio for the **MAIDS** group was significantly greater than the Control group (see Figure, $p<0.001$). The O/I for the **MAIDS** also significantly increased with time ($P<0.001$). These findings suggest that **MAIDS** impairs the normal function of the coronary microcirculation.

2001
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Set	Items	Description
S1	2763	(MOUSE OR MURINE) AND ACQUIRED AND IMMUNODEFICIENCY AND SYNDROME
S2	487	S1 AND MAIDS
S3	23	S2 AND PY>2000
S4	18	RD (unique items)
S5	5	S2 AND REVIEW?
S6	5	RD (unique items)
S7	17	S4 NOT S5

? s s6/3,ab/all
>>>Invalid syntax
? t s6/3,ab/all

6/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11254815 21291555 PMID: 11398815
Tsl and LP-BM5: a comparison of two **murine** retrovirus models for HIV.
Clark S; Duggan J; Chakraborty J
Department of Physiology and Molecular Medicine, Medical College of Ohio, Toledo 43614-5804, USA.
Viral immunology (United States) Jun 2001, 14 (2) p95-109, ISSN 0882-8245 Journal Code: 8801552
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ts1 **murine** leukemia virus produces an **immunodeficiency** state in mice that parallels human **immunodeficiency** virus (HIV) infection in humans. Other **murine** leukemia viruses, such as LP-BM5 used in the **murine acquired** immune deficiency virus (**MAIDS**) model, have been studied extensively as a small animal model for HIV research, but lack many key similarities to HIV. Mice infected with ts1, however, utilize CD4 target cells for infection, undergo neuronal loss and demyelination, and develop clinical **immunodeficiency** . These features make this retrovirus in many ways an ideal candidate for a small animal model for HIV research. In this **review** article, the early development, the molecular and clinical pathogenesis of both the ts1 mutant of the Moloney **murine** leukemia virus and LP-BM5 are examined. Based on an extensive evaluation of the literature on LP-BM5 and ts1, it is concluded that the ts1 virus may serve as a better animal model to human retrovirus infection.

6/3,AB/2 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09814100 BIOSIS NO.: 199598269018
Cytomegalovirus retinitis during AIDS: Current issues and future directions.
AUTHOR: Dix Richard D(a); Cray Carolyn; Cousins Scott
AUTHOR ADDRESS: (a)Dep. Ophthalmol., Bascom Palmer Eye Inst., Univ. Miami Sch. Med., Miami, FL 33101**USA
JOURNAL: Regional Immunology 6 (1-2):p112-118
ISSN: 0896-0623
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytomegalovirus (CMV) retinitis is the leading cause of blindness in patients with **acquired** immune deficiency **syndrome** (AIDS). Before improved therapeutic approaches can be developed to manage this devastating sight-threatening disease, specific questions pertinent to the pathophysiology of CMV retinitis must be addressed. These questions relate to the origin of virus responsible for retinitis, spread of virus within the retina, the immunopathogenesis of retinal destruction, and the fate of virus during traditional antiviral therapy. In this **review**, we examine for each question the clinical rationale, the experimental data, and the clinical implications associated with these data. In particular, two experimental systems are emphasized. One is an in vitro system to study the susceptibility of human retinal pigment epithelium to CMV infection. The other involves clinically-relevant **murine** models of CMV retinitis, especially one of retrovirus-induced **immunodeficiency** (**MAIDS**). We suggest that immune-based therapy alone or in combination with traditional chemotherapy offers improved prospects for maintaining subclinical CMV infection in the immunosuppressed individual, thereby preventing CMV retinitis.

6/3,AB/3 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08341318 BIOSIS NO.: 000043073441
RETROVIRUS-INDUCED **IMMUNODEFICIENCY** IN THE **MOUSE MAIDS** AS A MODEL FOR AIDS
AUTHOR: MORSE H C III; CHATTOPADHYAY S K; MAKINO M; FREDRICKSON T N; HUGIN A W; HARTLEY J W
AUTHOR ADDRESS: BUILD. 7, ROOM 304, NATL. INST. HEALTH, BETHESDA, MD. 20892.
JOURNAL: AIDS (PHILA) 6 (7). 1992. 607-621. 1992
CODEN: AIDSE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1992

6/3,AB/4 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07758547 BIOSIS NO.: 000041056798
MURINE ACQUIRED IMMUNODEFICIENCY SYNDROME **MAIDS** AN ANIMAL MODEL TO STUDY THE AIDS PATHOGENESIS
AUTHOR: JOLICOEUR P
AUTHOR ADDRESS: LAB. MOL. BIOL., CLINICAL RES. INST. MONTREAL, 110 PINE AVE. W., MONTREAL, QUEBEC, CAN. H2W 1R7.
JOURNAL: FASEB (FED AM SOC EXP BIOL) J 5 (10). 1991. 2398-2405. 1991
FULL JOURNAL NAME: FASEB (Federation of American Societies for Experimental Biology) Journal
CODEN: FAJOE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1991

6/3,AB/5 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06834529 BIOSIS NO.: 000038006753
PATHOGENESIS OF **MAIDS** A RETROVIRUS-INDUCED **IMMUNODEFICIENCY** DISEASE OF MICE
AUTHOR: CHATTOPADHYAY S K; MAKINO M; HARTLEY J W; MORSE H C III
AUTHOR ADDRESS: LAB. IMMUNOPATHOL., NATL. INST. ALLERGY AND INFECTIOUS DISEASES, NATL. INST. HEALTH, BUILD. 7, ROOM 302, BETHESDA, MD. 20892, USA.
JOURNAL: WU, B.-Q. AND J. ZHENG (ED.). IMMUNE-DEFICIENT ANIMALS IN EXPERIMENTAL MEDICINE; 6TH INTERNATIONAL WORKSHOP, BEIJING, CHINA, JULY 3-6, 1988. XIV+361P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, NEW YORK, USA. ILLUS. ISBN 3-8055-4934-2. 0 (0). 1989. 12-18. 1989
CODEN: 28286
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1989

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          100172  CAMP human?
          100172  S1
        13765360  HUMAN?
      S2   32885  S1 AND HUMAN?
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           32885  S2
          395036  ADMINISTER?
      S3     454  S2 AND ADMINISTER?
? s s3 and pharmaceutical?
             454  S3
          184093  PHARMACEUTICAL?
      S4       0  S3 AND PHARMACEUTICAL?
? s s3 and antagonist?
             454  S3
          592866  ANTAGONIST?
      S5      63  S3 AND ANTAGONIST?
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...examined 50 records  (50)
...completed examining records
      S6      51  RD (unique items)
? s s6 and immuno?
>>>File 155 processing for IMMUNO? stopped at IMMUNOFERMENTNOE
>>>File 5 processing for IMMUNO? stopped at IMMUNOFLUORESCENCES
              51  S6
          913614  IMMUNO?
      S7       1  S6 AND IMMUNO?
? s s6 and treat?
              51  S6
         3263219  TREAT?
      S8      21  S6 AND TREAT?
? t s8/3,ab/all

 8/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13509557   22126152   PMID: 12130738
  SL65.0155, a novel 5-hydroxytryptamine(4) receptor partial agonist with
potent cognition-enhancing properties.
  Moser Paul C; Bergis Olivier E; Jegham Samir; Lochead Alistair;
Duconseille Elee; Terranova Jean-Paul; Caille Dominique; Berque-Bestel
Isabelle; Lezoualc'h Frank; Fischmeister Rodolphe; Dumuis Aline; Bockaert
Joel; George Pascal; Soubrie Philippe; Scatton Bernard
  Sanofi-Synthelabo Recherche, 31 avenue Paul Vaillant Couturier, 92220
Bagneux, France.
  Journal of pharmacology and experimental therapeutics (United States)
Aug 2002, 302 (2) p731-41, ISSN 0022-3565 Journal Code: 0376362
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  SL65.0155 [5-(8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-3-[1-(2-
phenyl ethyl)-4-piperidinyl]-1,3,4-oxadiazol-2(3H)-one monohydrochloride]
is a novel benzodioxanoxadiazolone compound with high affinity for
human 5-hydroxytryptamine (5-HT)(4) receptors (K(i) of 0.6 nM) and
good selectivity (greater than 100-fold for all other receptors tested). In
cells expressing the 5-HT(4(b)) and 5-HT(4(e)) splice variants, SL65.0155
acted as a partial agonist, stimulating cAMP production with a
maximal effect of 40 to 50% of serotonin. However, in the rat esophagus
preparation, SL65.0155 acted as a 5-HT(4) antagonist with a pK(b) of
8.81. In addition, SL65.0155 potently improved performance in several tests
of learning and memory. In the object recognition task, it improved
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Human reproduction (Oxford, England) (ENGLAND) Apr 1999, 14 (4) p885-8, ISSN 0268-1161 Journal Code: 8701199
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Gonadotrophin-releasing hormone (GnRH) regulates gonadotrophin release. It has been shown that GnRH may have a direct effect on the ovary, as the addition of GnRH to granulosa cell cultures inhibits the production of progesterone and oestradiol. Specific GnRH receptors have been found to be present in rat and **human** granulosa cells. Desensitization of the pituitary by GnRH agonist has become common in in-vitro fertilization (IVF) **treatment** , usually by a long protocol of 2-3 weeks. With the introduction of GnRH **antagonists**, which produce an immediate blockage of the GnRH receptors, a much shorter exposure is needed of 3-6 days. The aim of this study was to evaluate the effect of a GnRH agonist (buserelin) and a GnRH **antagonist** (cetrorelix) on the function of granulosa cells cultured in vitro from IVF patients. Women were **treated** by IVF randomized either to have buserelin nasal spray from the luteal phase in the previous cycle or cetrorelix from day 6 of the cycle. Both groups had ovarian stimulation with **human** menopausal gonadotrophin (HMG) 150 IU daily, i.e. HCG was **administered** when the follicles were larger than 17 mm, and aspirated 36 h later. Granulosa cells, separated and washed from large follicles containing ova, were pooled. After 48 h of pre-incubation, the granulosa cells were cultured for 4 days in medium with either added testosterone or **cAMP** with or without HCG, with change of medium after 2 days. The progesterone and oestradiol concentrations in the culture medium were measured by immunological assay, and cellular protein was measured by microprotein assay. The results showed that granulosa cells from women **treated** with GnRH **antagonist** (cetrorelix) responded earlier to the in-vitro hormone stimulation in terms of progesterone accumulation than women **treated** with the GnRH agonist (buserelin). This may have been due to difference in time of exposure to the analogue. The results may indicate that the luteal function is less impaired in GnRH **antagonist treatment** than in GnRH agonist **treatment**.

8/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10138607 99103929 PMID: 9886979
A novel plant-derived inhibitor of **cAMP**-mediated fluid and chloride secretion.
Gabriel S E; Davenport S E; Steagall R J; Vimal V; Carlson T; Rozhon E J
Department of Pediatric Gastroenterology, University of North Carolina, Chapel Hill, North Carolina 27599, USA.
American journal of physiology (UNITED STATES) Jan 1999, 276 (1 Pt 1) pG58-63, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: P30-DK-34987; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have identified an agent (SP-303) that shows efficacy against in vivo cholera toxin-induced fluid secretion and in vitro **cAMP**-mediated Cl- secretion. Administration of cholera toxin to adult mice results in an increase in fluid accumulation (FA) in the small intestine (FA ratio = 0.63 vs. 1.86 in control vs. cholera toxin-**treated** animals, respectively). This elevation in FA induced by cholera toxin was significantly reduced (FA ratio = 0.70) in animals **treated** with a 100 mg/kg dose of SP-303 at the same time as the cholera **treatment**. Moreover, when SP-303 was **administered** 3 h after cholera toxin, a dose-dependent inhibition of FA levels was observed with a half-maximal inhibitory dose of 10 mg/kg. In

Ussing chamber studies of Caco-2 or T84 monolayer preparations, SP-303 had a significant effect on both basal current and forskolin-stimulated Cl- current. SP-303 also induced an increase in resistance that paralleled the observed decrease in current. These data suggest that SP-303 has an inhibitory effect on **cAMP** -mediated Cl- and fluid secretion. Thus SP-303 may prove to be a useful broad-spectrum antidiarrheal agent.

8/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10130550 99112688 PMID: 9915482
Expression and possible functional role of the beta3-adrenoceptor in **human** and rat detrusor muscle.
Fujimura T; Tamura K; Tsutsumi T; Yamamoto T; Nakamura K; Koibuchi Y; Kobayashi M; Yamaguchi O
Fujisawa Research Institute of America, Inc., Evanston, Illinois 60201, USA.
Journal of urology (UNITED STATES) Feb 1999, 161 (2) p680-5, ISSN 0022-5347 Journal Code: 0376374
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To investigate the presence of the beta3-adrenoceptor (beta3-AR) in **human** and rat detrusor muscle and the usefulness of beta3-AR agonists as drugs for the **treatment** of urinary frequency. MATERIALS AND METHODS: FK175, ethyl [(S)-8-[(R)-2-(3-chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrah ydro-5H-benzocyclohepton-2-yloxy]acetate monohydrochloride monohydrate, was used as a beta3-AR selective agonist. The expression of beta-AR subtypes (beta1-, beta2-, beta3-AR) mRNA was investigated in rat and **human** detrusor muscle by RT-PCR. Beta3-AR agonist induced cyclic AMP (**cAMP**) levels were measured in rat detrusor muscle strips. The relaxation response produced by a beta3-AR agonist was measured in a KCl induced tonic contraction model in rat detrusor muscle strips. The effect of a beta3-AR agonist on urinary bladder function was investigated by cystometry using a conscious rat model of urinary frequency. RESULTS: beta3-AR mRNA was substantially expressed in both rat and **human** detrusor muscles. The beta3-AR agonist, FK175 (10(-7) M), increased the **cAMP** level by 30% in rat detrusor muscle. In isolated rat detrusor muscle strips contracted with KCl, the beta3-AR agonist, FK175 (10(-8) to 10(-4) M), produced a concentration-dependent relaxation. Moreover, although the relaxation induced with FK175 was blocked by the non-selective beta-AR **antagonist** , bupranolol, it was unaffected by ether the beta1-AR selective **antagonist**, CGP 20712A, or the beta2-AR selective **antagonist** , ICI 118551, suggesting that FK175 induced the relaxation via the beta3-AR. Furthermore, in the rat model, the orally **administered** beta3-AR agonist, FK175 (10 mg./kg.) significantly increased bladder capacity with no change of micturition pressure or threshold pressure. CONCLUSIONS: These results suggest that beta3-AR agonists may be effective in the **treatment** of urinary frequency.

8/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10059123 99037243 PMID: 9819808
A therapeutic strategy to prevent morphine dependence and tolerance by coadministration of **cAMP**-related reagents with morphine.
Itoh A; Noda Y; Mamiya T; Hasegawa T; Nabeshima T
Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University School of Medicine, Japan.
Methods and findings in experimental and clinical pharmacology (SPAIN) Sep 1998, 20 (7) p619-25, ISSN 0379-0355 Journal Code: 7909595

Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Morphine is the most potent opioid analgesic currently available and its use is increasing for **treatment** of severe pain, however, long-term morphine exposure induces physical dependence/tolerance. Although the mechanisms underlying this phenomenon have not been established, several biochemical changes including intracellular **cAMP** systems and Ca2+ mobilization have been suggested. To evaluate the contribution of **cAMP**, we investigated the effects of nefiracetam [N-(2,6-dimethyl-phenyl)-2(2-oxo-1-pyrrolidinyl)acetamide] and phosphodiesterase inhibitors (theophylline, enprofylline and rolipram) on the development of morphine dependence/tolerance. Mice **administered** morphine (6 or 10 mg/kg, s.c.) twice daily for 5 days, showed withdrawal signs (jumping, diarrhea and body weight loss) after naloxone challenge (5 mg/kg, i.p.), indicating the physical dependence to morphine. Further, the tolerance to antinociceptive effect of morphine was observed in these mice on the tail-flick test. However, coadministration of nefiracetam (5 or 10 mg/kg, p.o.), enprofylline (30 mg/kg, p.o.) and rolipram (0.3 or 1 mg/kg, i.p.) with morphine during the pretreatment period, significantly reduced the withdrawal signs, moreover, the tolerance was significantly attenuated. Acute administration of nefiracetam failed to reduce the withdrawal signs and did not affect the antinociceptive effect of morphine in morphine-naive mice. Theophylline (3 or 10 mg/kg, p.o.) tended to attenuate the development of morphine dependence/tolerance. The present findings suggest that coadministration of compounds which increase **cAMP** level with morphine may be a useful strategy to attenuate the development of morphine dependence/tolerance in the clinic.

8/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09915541 98357884 PMID: 9694511

Prostaglandin E2 inhibits apoptosis in **human** neutrophilic polymorphonuclear leukocytes: role of intracellular cyclic AMP levels.

Ottonello L; Gonella R; Dapino P; Sacchetti C; Dallegri F
First Medical Clinic, Department of Internal Medicine, University of Genoa Medical School, Italy.

Experimental hematology (UNITED STATES) Aug 1998, 26 (9) p895-902, ISSN 0301-472X Journal Code: 0402313
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Human neutrophilic polymorphonuclear leukocytes (neutrophils) are terminally differentiated cells that die by undergoing apoptosis. At present, the intracellular pathways governing this process are only partially known. In particular, although the adenylate cyclase-dependent generation of cyclic AMP (**cAMP**) has been implicated in the triggering of apoptosis in lymphoid cells, the role of the intracellular **cAMP** pathway in neutrophil apoptosis remains controversial. In the present study, we found that two **cAMP**-elevating agents, prostaglandin E2 (PGE2) and the phosphodiesterase type IV inhibitor RO 20-1724, inhibit neutrophil apoptosis without inducing cell necrosis. When **administered** in combination, PGE2 and RO 20-1724 displayed additive effects. Moreover, neutrophil apoptosis was inhibited by a membrane-permeable analog of **cAMP**, dibutyryl-**cAMP**, in a dose-dependent manner. Finally, **treatment** of neutrophils with the protein kinase A inhibitor H-89 prevented PGE2- and RO 20-1724-induced inhibition of cell apoptosis. In conclusion, taking into account that PGE2 and other **cAMP**-elevating agents are well known downregulators of neutrophil functions, our results suggest that conditions favoring a state

of functional rest, such as intracellular **cAMP** elevation, prolong the life span of neutrophils by delaying apoptosis.

8/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09907109 98322534 PMID: 9658398
Hormone-induced proliferation and differentiation of granulosa cells: a coordinated balance of the cell cycle regulators cyclin D2 and p27Kip1.
Robker R L; Richards J S
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Jul 1998, 12 (7) p924-40, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: HD-16272; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The proliferation and terminal differentiation of granulosa cells are critical for normal follicular growth, ovulation, and luteinization. Therefore, the in situ localization and hormonal regulation of cell cycle activators (cyclin D1, D2, and D3) and cell cycle inhibitors (p27Kip1 and p21Cip1) were analyzed in ovaries of mice and rats at defined stages of follicular growth and differentiation. Cyclin D2 mRNA was specifically localized to granulosa cells of growing follicles, while cyclin D1 and cyclin D3 were restricted to theca cells. In hypophysectomized (H) rats, cyclin D2 mRNA and protein were increased in granulosa cells by **treatment** with estradiol or FSH and were increased maximally by **treatment** with both hormones. In serum-free cultures of rat granulosa cells, cyclin D2 mRNA was rapidly elevated in response to FSH, forskolin, and estradiol, indicating that estradiol as well as **cAMP** can act directly and independently to increase cyclin D2 expression. The levels of p27Kip1 protein were not increased in response to estradiol or FSH. In contrast, when ovulatory doses of **human** CG (LH) were **administered** to hormonally primed H rats to stimulate luteinization, cyclin D2 mRNA and protein were rapidly decreased and undetectable within 4 h, specifically in granulosa cells of large follicles. Also in response to LH, the expression of the cell cycle inhibitor p27Kip1 was induced between 12 and 24 h (p21Cip1 was induced within 4 h) and remained elevated specifically in luteal tissue. A critical role for cyclin D2 in the hormone-dependent phase of follicular growth is illustrated by the ovarian follicles of cyclin D2-/- mice, which do not undergo rapid growth in response to hormones, but do express markers of FSH/LH action, cell cycle exit, and terminal differentiation. Collectively, these data indicate that FSH and estradiol regulate granulosa cell proliferation during the development of preovulatory follicles by increasing levels of cyclin D2 relative to p27Kip1 and that LH terminates follicular growth by down-regulating cyclin D2 concurrent with up-regulation of p27Kip1 and p21Cip1.

8/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09891297 98324155 PMID: 9653071
Effect of a dopamine agonist on luteinizing hormone receptors, cyclic AMP production and steroidogenesis in rat Leydig cells.
Dirami G; Cooke B A
Department of Biochemistry and Molecular Biology, Royal Free Hospital School of Medicine, London, England, United Kingdom.
Toxicology and applied pharmacology (UNITED STATES) Jun 1998, 150 (2) p393-401, ISSN 0041-008X Journal Code: 0416575

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Dopamine agonists are known to increase the incidence of Leydig cell hyperplasia/adenomas when **administered** to rats over periods of 1-2 years. We have examined the early changes in factors affecting luteinizing hormone (LH)-controlled signal transduction pathways and steroidogenesis in Leydig cells in vitro after chronic oral administration of one of these dopamine agonists, Mesulergine (CU327-085) (N-(1-6,dimethylergolin-8a-yl)-N',N'-dimethylsulphamide hydrochloride) to Sprague-Dawley (SD) rats. Eight-week-old rats were given this dopamine agonist (2 mg/kg body wt/day) in food for 1, 5, or 12 weeks. The Leydig cells from control and **treated** rats were purified by elutriation and density gradient centrifugation. The dopamine agonist **treatment** was found to decrease the specific binding of 125I-**human** chorionic gonadotrophin (hCG) binding to the Leydig cells: a decrease was detected as early as 1 week after **treatment** and was more pronounced after 5 and 12 weeks. This was found to be due to a decrease in the LH/hCG receptor numbers and not to a decrease in LH/hCG-receptor binding affinity. Both basal and LH-stimulated **cAMP** and testosterone production were also decreased; **cAMP** production was decreased by approximately 50% by all concentrations of LH added whereas testosterone production was only decreased with submaximum stimulating concentrations of LH. The formation of testosterone in response to dibutyryl **cAMP** was also decreased by approximately 50%, indicating additional lesions in the signal transduction pathway. The addition of the cell permeant 22R-hydroxycholesterol (22R) demonstrated that testosterone but not pregnenolone production was decreased by **treatment** with the dopamine agonist, thus indicating that the 17 alpha-hydroxylase/C17-20 lyase may have been inhibited. Supporting evidence for this was found because the dopamine agonist also increased aromatase activity in the Leydig cells and thus the potential to produce estrogens; previous studies have shown that estradiol is an inhibitor of the 17-20 lyase enzyme. The addition of the dopamine agonist directly to the Leydig cells did not inhibit **cAMP** production or testosterone production except at high concentrations. It is concluded that **treatment** of rats with the dopamine agonist indirectly (i.e., via the pituitary) affects Leydig cell function resulting in a rapid decrease in LH receptors and **cAMP** and testosterone production. Aromatase activity is increased and thus the capacity to produce estrogens. These early changes in the signal transduction pathways and steroidogenesis may be involved in the Leydig cell hyperplasia/adenoma formation that subsequently occurs.

8/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08055902 94185547 PMID: 8137736
The coupling of multiple signal transduction pathways with steroid response mechanisms.
Nordeen S K; Moyer M L; Bona B J
Department of Pathology, University of Colorado Health Sciences Center, Denver 80262.
Endocrinology (UNITED STATES) Apr 1994, 134 (4) p1723-32, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK-37061; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

In a **human** breast carcinoma-derived cell line engineered to contain a hormone-responsive luciferase reporter gene, manipulation of cell growth conditions or cellular signal transduction in a variety of ways can enhance or impair glucocorticoid-mediated induction of a target gene. Induction may

be enhanced as much as 10-fold or inhibited 90% by different **treatments** . For example, two different inhibitors of protein phosphatase-1 and -2A potentiated the hormone-dependent induction of luciferase. Activation of protein kinase-A via addition of 8-bromo-**cAMP** or forskolin also potentiated the hormonal induction, whereas 8-bromo-cGMP was ineffective. In contrast, activating protein kinase-A by inhibiting **cAMP** turnover with the phosphodiesterase inhibitors isobutylmethylxanthine or Ro20-1724 inhibited the hormone response rather than potentiated it. The inhibitory activity of isobutylmethylxanthine was evident even when activators of protein kinase-A are **administered** simultaneously. Isobutylmethylxanthine must, therefore, activate a signal transduction pathway in addition to the protein kinase-A pathway. Activation of protein kinase-C potentiated the hormone response in a cell-specific manner. **Treatment** with epidermal growth factor and imposition of cell stress by heat shock or inhibition of protein synthesis also enhanced the glucocorticoid response. Thus, our results suggest an elaborate coupling of the steroid response pathway with other cellular signal transduction mechanisms that permits an additional layer of control to be imposed on hormone-mediated transcriptional responses. It is proposed that cell-specific phosphorylation events influence steroid receptor interaction with the basal transcription apparatus, thereby altering receptor-mediated induction mechanisms.

8/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07617164 93140026 PMID: 8380866

Buprenorphine prevents and reverses the expression of chronic etorphine-induced sensitization of adenylyl cyclase in SK-N-SH **human** neuroblastoma cells.

Thomas J M; Hoffman B B

Department of Medicine, Stanford University School of Medicine, Palo Alto, California.

Journal of pharmacology and experimental therapeutics (UNITED STATES) Jan 1993, 264 (1) p368-74, ISSN 0022-3565 Journal Code: 0376362

Contract/Grant No.: AG09597; AG; NIA

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Buprenorphine is an opiate drug with a mixed agonist-**antagonist** profile and has therapeutic efficacy in attenuating drug craving and addiction. Because the adenylyl cyclase system has been implicated in the biochemical basis of opiate withdrawal phenomena, we have compared the acute and chronic effects of buprenorphine with the full opiate agonist etorphine on cyclic AMP (**cAMP**) synthesis in the **human** neuroblastoma cell SK-N-SH. Both drugs acutely inhibited prostaglandin (PG)E1-stimulated **cAMP** accumulation; the inhibition caused by either drug was prevented by pretreatment with the opiate **antagonist** naltrexone or with pertussis toxin. Chronic **treatment** of the cells with etorphine induced an increase in PGE1-stimulated **cAMP** synthesis which was observed after withdrawal of the inhibitory drug. Chronic **treatment** with buprenorphine appeared to have the opposite effect, resulting in an attenuated PGE1 stimulation; additionally, buprenorphine prevented the etorphine-induced enhancement in **cAMP** synthesis, whether **administered** before or after prolonged incubation of the cells with etorphine. The attenuating effect of buprenorphine occurred within 5 min and was prevented by a prior application of naltrexone, but could not be reversed by a subsequent **treatment** with **antagonist** . These findings suggest that buprenorphine was binding (pseudo)irreversibly to the opiate receptor, resulting in a persistent inhibition of **cAMP** synthesis which masks the etorphine-induced enhancement of adenylyl cyclase activity. This hypothesis was confirmed by

experiments demonstrating that **treatment** of the cells with buprenorphine significantly reduced available opiate receptor binding sites despite extensive washing of the cells to remove unbound buprenorphine. These pharmacodynamic actions of buprenorphine may be relevant to its therapeutic efficacy in **treating** drug abuse and addiction.

8/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07234703 92170638 PMID: 1665308
The bronchodilator action of AH 21-132.
Small R C; Foster R W; Berry J L; Chapman I D; Elliott K R
Department of Physiological Sciences, University of Manchester.
Agents and actions. Supplements (SWITZERLAND) 1991, 34 p3-26, ISSN 0379-0363 Journal Code: 7801014
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The benzonaphthyridine derivative, AH 21-132, has non-specific relaxant effects in isolated airways smooth muscle. The action of AH 21-132 in trachealis muscle is not antagonised by propranolol but AH 21-132 is slightly potentiated by epithelium removal. Electrophysiological recording from guinea-pig trachealis shows that AH 21-132-induced relaxation is accompanied by suppression of electrical slow waves and by cellular hyperpolarisation. Unlike theophylline, AH 21-132 does not cause spasm of cooled (12 degrees C), indomethacin-**treated** trachealis muscle, nor does it act as an **antagonist** at adenosine A1 receptors. AH 21-132 does not depress the Ca2+ sensitivity or responsiveness of Triton X-100 skinned trachealis fibres. In tracheal relaxant concentrations, AH 21-132 selectively inhibits **cAMP** phosphodiesterase (PDE) compared with cGMP-PDE. The (-)-enantiomer of AH 21-132 is more potent than its (+)-enantiomer both in causing tracheal relaxation and in inhibiting **cAMP** -PDE. When tested on PDE isoenzymes separated from bovine trachealis and guinea-pig cardiac ventricles, AH 21-132 exhibits selectivity as an inhibitor of the isoenzyme types III and IV. AH 21-132 increases the trachealis content of **cAMP** and cGMP, but only in concentration greater than that required fully to suppress the mechanical tone of the tissue. AH 21-132 has bronchodilator activity in anaesthetised, ventilated guinea-pigs when **administered** intraduodenally, intravenously or by inhalation. Inhaled AH 21-132 also provides bronchodilatation in healthy **human** volunteers in whom bronchoconstriction has been induced by inhaled methacholine.

8/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07180723 92118228 PMID: 1768353
The **treatment** of hyperkalemia with salbutamol]
Tratamiento de la hiperkalemia con salbutamol.
Velasquez L; Munoz R
Departamento de Nefrologia, Hospital Infantil de Mexico Federico Gomez, D.F.
Boletin medico del Hospital Infantil de Mexico (MEXICO) Nov 1991, 48 (11) p775-9, ISSN 0539-6115 Journal Code: 0414106
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: SPANISH
Main Citation Owner: NLM
Record type: Completed
For several years now, it has been known that the **administering** of adrenergic beta **antagonists** , especially of the beta-2 type, induce

hypokalemia as a result of the entering of potassium into the skeletal muscle cells. This fall in kalemia occurs independently from the effect of insulin, aldosterone or kidney excretion, is mediated by the beta-2 receptors and require the intervention of **cAMP** joined at the cell membrane and the subsequent stimulation of the Na-K-ATPase which bring the potassium into the striated muscle cell. Among the most outstanding drugs with beta-2 effect is salbutamol, which maintains the hypokalemic effect whether **administered** intravenously or inhaled. It has been used in cases of hyperkalemia, in both children and adults. The initially used intravenous dosage (0.5 mg) caused several side-effects, especially rapid heart beat, seen more in children. It has been recently found that the use of doses as low as 4 micrograms/kg lower the kalemia to values averaging 1.4 to 1.6 mEq/L (mmol/L); in addition, using these dosages intravenously in an average of 20 minutes, no side-effects were seen, even when **administered** to newborns. For the above, we considered that salbutamol, in the suggested dosages, constitutes an efficient and secure therapeutic method for the initial **treatment** of severe hyperkalemic patients.

8/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04830382 85198135 PMID: 6100037
Effects of the antiestrogen CI-628 on hCG-induced desensitization of testosterone in purified Leydig cells.
Keel B A; Melner M H; Abney T O
Archives of andrology (UNITED STATES) 1984, 13 (1) p71-5, ISSN 0148-5016 Journal Code: 7806755
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effect of CI-628 on **human** chorionic gonadotropin-induced desensitization of testosterone production was investigated. Purified Leydig cells were isolated from mature male rats 24 hr postinjection with (1) 30 of 300 IU hCG s.c., (2) 1 mg CI-628 i.p., or (3) CI-628 pretreatment plus hCG. Steroidogenic desensitization to Bt2 **cAMP** and hCG stimulation in vitro was observed with both doses of hCG **administered** in vivo. CI-628 **treatment** alone led to an increased basal production but an unaltered maximum production of testosterone obtained in the presence of hCG or Bt2 **cAMP** in vitro. CI-628 in combination with hCG **treatment** in vivo led to testosterone production in vitro that was similar to that observed with hCG **treatment** alone. CI-628 does not inhibit the hCG-induced desensitization of testosterone production, and the results do not support a role of estrogen receptors in this process.

8/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03914282 82190235 PMID: 6281294
Cimetidine **treatment** of azotemic secondary hyperparathyroidism.
Robinson M F; Johnson W J; Heath H
Journal of clinical endocrinology and metabolism (UNITED STATES) Jun 1982, 54 (6) p1206-9, ISSN 0021-972X Journal Code: 0375362
Contract/Grant No.: AM-19607; AM; NIADDK; AM-27440; AM; NIADDK; RR-585; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cimetidine, an **antagonist** to histamine H2-receptors, reportedly lowers serum calcium and/or serum immunoreactive parathyroid hormone (iPTH)

concentrations in some patients with primary and secondary (azotemic) hyperparathyroidism. We **administered** the drug orally (300 mg every 6 h) to five normal volunteers and four azotemic patients with secondary hyperparathyroidism who were not undergoing chronic hemodialysis. The normal persons and one azotemic patient took the drug for 5 weeks, and the remaining azotemic patients took it for 1 week. Before **treatment**, all patients had elevated levels of serum iPTH (two different assay systems), with or without elevated serum calcium concentrations, and increased urinary excretion of **cAMP** (per 100 ml glomerular filtrate). Cimetidine **treatment** caused no changes in serum calcium, phosphorus, or iPTH or in urinary **cAMP** (expressed as nanomoles per g creatinine). Serum creatinine, however, increased significantly in patients (P less than 0.02) and control subjects (P less than 0.025), which yielded statistically significant but spurious increases of urinary **cAMP** when expressed per 100 ml glomerular filtrate. We conclude that short term cimetidine administration has no effect on parathyroid function in normal persons or those with azotemic hyperparathyroidism. Because of its confusing effect on serum creatinine and a possible (albeit rare) adverse effect on renal function, the drug should be used with caution in azotemic patients not yet requiring chronic dialysis.

8/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

02718650 78023598 PMID: 199407
Cyclic adenosine 3',5'-monophosphate, adenylate cyclase and physical dependence on ethanol: studies with tranylcypromine.
Shen A; Ansky A J; Smith T; Pathman D; Thurman R G
Drug and alcohol dependence (SWITZERLAND) Sep-Nov 1977, 2 (5-6) p431-40, ISSN 0376-8716 Journal Code: 7513587
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tranylcypromine, a monoamine oxidase inhititor, was **administered** to rats during chronic ethanol **treatment** . The severity of the hyperactive withdrawal behavior observed upon removal of ethanol was, during the first 60 hours of **treatment**, similar in both ethanol and ethanol + tranylcypromine **treated** animals. However, after 84 hours of ethanol **treatment**, tranylcypromine slightly depressed the withdrawal severity. Rises in cerebral cortical cyclic adenosine 3',5'-monophosphate (**cAMP**) levels and adenylate cyclase activity associated with withdrawal behavior in ethanol-**treated** rats, though, were not observed. (Adenylate cyclase activity used throughout this paper refers to % conversion of 3H-adenine into 3H-**cAMP**). Based on this and previous data, a model invoking two neurochemical adaptations--one in adenylate cyclase and one, as yet, unknown-is proposed for the mechanism of physical dependence.

8/3,AB/17 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12533225 BIOSIS NO.: 200000286727
Treatment of polycystic kidney disease using vasopressin V2 receptor **antagonists**.
AUTHOR: Gattone Vincent H(a)
AUTHOR ADDRESS: (a)Overland Park, KS**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1227 (4):pNo pagination Oct. 26, 1999
MEDIUM: e-file.
ISSN: 0098-1133

DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention is directed to the novel **treatment** of ARPKD and ADPKD by **administering** a pharmacologically effective amount of a V2 receptor **antagonist**. Orally active V2 receptor **antagonists** such as OPC-31260, OPC-41061, SR121463A and VPA-985 are **administered** alone, or in combination to mammalian PKD subjects to reduce the **cAMP** generated by the increased expression of AVP-V2 receptor, AQP2 and AQP3, thereby reducing and/or preventing cyst enlargement.

1999

8/3,AB/18 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09861247 BIOSIS NO.: 199598316165
LH-RH and its **antagonist** Cetrorelix inhibit growth of JAR **human** choriocarcinoma cells in vitro.
AUTHOR: Horvath Judit E; Ertl Tibor; Qin Yunfeng; Groot Kate; Schally Andrew V(a)
AUTHOR ADDRESS: (a)VA Med. Cent., 1601 Perdido Street, New Orleans, LA 70146**USA
JOURNAL: International Journal of Oncology 6 (5):p969-975 1995
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of luteinizing hormone-releasing hormone (LH-RH), and LH-RH **antagonist** Cetrorelix, (SB75, (Ac-D-Nal(2)-1,D-Phe(4-Cl)-2,D-Pal(3)-3,D-Cit-6,D- Ala-10)LH-RH) on cell growth and the production of hCG and **cAMP** in JAR **human** choriocarcinoma cells were examined in vitro. Both LH-RH and its **antagonist** SB-75, at 1 mu-g concentration, inhibited the growth of JAR cells in cultures. When SB-75 (1 mu-M) was given in combination with different doses (0.1 nM to 1 mu-M) of LH-RH, it was found that 0.1 nM LH-RH nullified the inhibitory effect of SB-75 on cell growth, however, the 100 nM and 1 mu-M doses of LH-RH caused a greater inhibition of cell proliferation than SB-75 alone. Incubation with LH-RH slightly increased the hCG production and the **cAMP** release in the cultured tumor cells. SB-75 alone or in combination with LH-RH reduced the hCG as well as the **cAMP** release from JAR **human** choriocarcinoma cells; however, the magnitude of the decrease was smaller for hCG than for **cAMP**. The effect of different doses of LH-RH, **administered** simultaneously with 1 mu-M SB-75, on the **cAMP** production, was similar to that on cell growth: 0.1 nM LH-RH in combination with 1 mu-M SB-75 caused a smaller inhibition of **cAMP** than SB-75 alone. However, when LH-RH was given at concentrations from 1 nM to 1 mu-M together with 1 mu-M SB-75, we observed a greater inhibition of **cAMP** than after SB-75 alone. The presence of low affinity LH-RH receptors on JAR cells was also demonstrated and competitive binding studies showed that agonist D-Trp-6-LH-RH and **antagonist** SB-75 could bind to these receptors. Our findings provide new information on the effect of LH-RH and **antagonist** SB-75 on the proliferation of JAR **human** choriocarcinoma cells and may offer a new insight on their mechanisms of action in the suppression of tumor cell growth and their influence on intracellular signal transduction pathways. Hormonal therapy based on Cetrorelix could be considered for the development of new approaches to **treatment** of patients with choriocarcinomas.

1995

8/3,AB/19 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09136137 BIOSIS NO.: 199497144507
Effects of chronic lithium **treatments** on central dopaminergic receptor systems: G proteins as possible targets.
AUTHOR: Carli Martin; Anand-Srivastava Madhu B; Molina-Holgado Eduardo; Dewar Karen M; Reader Tomas A(a)
AUTHOR ADDRESS: (a)Dep. Physiol., Univ. Mont., C.P. 6128 Succursale A, Montreal, PQ H3C 3J7**Canada
JOURNAL: Neurochemistry International 24 (1):p13-22 1994
ISSN: 0197-0186
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Numerous biochemical and electrophysiological studies have proposed a role for dopamine (DA) in the therapeutic efficacy of lithium (Li+) salts. The effects of ex vivo chronic Li+ **treatments** on neostriatal DA receptors, as well as on the G protein adenylyl cyclase complex and on tissue **cAMP** levels were investigated in adult rats. The animals were **administered** LiCl in their drinking water (1 g/l) for varying periods of time, i.e. 1, 15 and 28 days. After sacrifice by decapitation, their brains were removed and the neostriatum dissected out to assay DA receptors and adenylyl cyclase activity. The **antagonists** (3H)SCH23390 and (3H)raclopride were employed to label D-1 and D-2 receptors, respectively. Chronic Li+ **treatments** did not modify the saturation binding of either ligand. However, competition studies of the same **antagonists** by DA revealed biphasic curves, and the inhibition constant of the high-affinity site was significatively increased after chronic Li+. The data suggest an alteration in the coupling efficacy between G proteins and DA receptors. Moreover, chronic (28 day) Li+ **treatment**, but not a 1 day Li+ administration, lead to a reduction of the GTP-induced and DA-sensitive adenylyl cyclase activity, without changes in the basal activity or in forskolin-induced **cAMP** production. The results demonstrate that chronic Li+ **treatments** diminish neostriatal dopaminergic activity, probably through a direct action on the G protein itself. The underlying mechanisms do not appear to involve modifications in either the D-1, or the D-2, receptor primary ligand recognition sites, but may represent alterations in both the coupling process and the capacity of the G proteins, once activated, to stimulate adenylyl cyclase.

1994

8/3,AB/20 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07657968 BIOSIS NO.: 000092015389
INFLUENCE OF PINEAL INDOLEAMINES ON THE MITOTIC ACTIVITY OF GASTRIC AND COLONIC MUCOSA EPITHELIAL CELLS IN THE RAT INTERACTION WITH OMEPRAZOLE
AUTHOR: LEWINSKI A; RYBICKA I; WAJS E; SZKUDLINSKI M; PAWLIKOWSKI M
AUTHOR ADDRESS: DEP. EXP. ENDOCRINOL. AND HORMONE DIAGNOSTICS, INST. ENDOCRINOL., MED. ACAD. LODZ, 91-425 LODZ, DR. STERLING STR. NO. 3, POLAND.
JOURNAL: J PINEAL RES 10 (2). 1991. 104-108. 1991
FULL JOURNAL NAME: Journal of Pineal Research

CODEN: JPRSE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have investigated the effects of melatonin (Mel) and N-acetylserotonin (NAc-5HT) on the mitotic activity of gastric and colonic mucosa in adult male rats under basal conditions and after an administration of omeprazole (OM) (H+,K+-ATPase inhibitor). The metaphase-arrest technique was applied in the study. Additionally, serum gastrin levels were measured by RIA method in the OM-**treated** group and in respective polyethyeleneglycol (PEG)-**administered** controls. We have found that: 1) OM-**treatment** increased serum gastrin levels in rats; 2) OM enhanced the mitotic activity of the colonic mucosa cells, although, unexpectedly, it did not exert such an effect on the gastric mucosa cells; 3) Mel suppressed the OM-induced increase of the colonic epithelium cell proliferation, while NAc-5HT failed to reveal that action; 4) NAc-5HT decreased the proliferation of gastric mucosa epithelial cells. The value of the mean mitotic activity rate (MMAR) of gastric mucosa after Mel-**treatment** also decreased, but that change was not statistically significant. The obtained data are in compliance with previous results from our laboratory concerning the inhibitory effect of pineal indoleamines on the jejunal epithelium mitotic activity. The stimulatory effect of OM on the proliferation of colonic epithelium is probably mediated by OM-induced hypergastrinaemia. The possibility of Mel interaction with intestinal gastrin receptors (a structural similarity occurs between Mel and benzotript, a specific gastrin receptor **antagonist**), as well as of the opposite effects of Mel and gastrin on intracellular **cAMP** content in the gut, are considered in the discussion of results.

1991

8/3,AB/21 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07310650 BIOSIS NO.: 000090090543
PICOTAMIDE PREVENTION AND **TREATMENT** OF DIABETIC VASCULAR DISEASE A DOUBLE-BLIND CLINICAL TRIAL
AUTHOR: PIBIRI L; PETRUZZO P; DE GIUDICI A; BROTZU G
AUTHOR ADDRESS: VIA STAMPA, 10-CAGLIARI.
JOURNAL: CLIN TER 133 (4). 1990. 233-237. 1990
FULL JOURNAL NAME: Clinica Terapeutica
CODEN: CLTEA
RECORD TYPE: Abstract
LANGUAGE: ITALIAN

ABSTRACT: Picotamide is the most interesting compound of 4-OH isophtalic acid. It is effective in vitro and in vivo. Picotamide induces inhibition of platelet aggregation: it is a thromboxane sinthetase inhibitor and a thromboxane receptor **antagonist**. Picotamide causes cyclic endoperoxide accumulation and diverts their metabolism toward PgI2 synthesis in endothelial cells. PGI2 stimulates the adenylate cyclase with **cAMP** synthesis which makes platelets less sensitive to aggregatory stimulation. Picotamide induces enhancement of fibrinolytic activity, with significant reduction in the level of circulating plasminogen but in the same time it does not affect antithrombin III and FDP levels. In the present study picotamide or placebo were **administered** in a double blind trial at 600 mg daily for six months to 51 patients effected by diabetic macro and/or microangiopathy. The patients were 38 men and 13 women, the age was between 20 and 80 years (mean age 62.34). Twenty-seven patients were affected by type I diabetes and 24 by type II diabetes. Twenty-three of these patients presented

macroangiopathic lesions, 9 only microangiopathic lesions and 13 both. Twenty-five patients received picotamide and the other 25 an identical placebo for six months. One patient manifested myocardial infarction during the wash-out period and failed to enter the study. The following determinations were carried out: at T0 clinical examination, Doppler ultrasonography, Winsor Index, laboratory parameters; after 90 days (T90) clinical examination and Winsor Index and after 180 days (T180) were repeated photopletysmography and clinical parameters too. Patients were not only evaluated for the vascular disease of lower extremities, but also for the other complications of diabetes, as retinopathy, nephropathy, cardiac and cerebrovascular disease. After six months we observed a significant improvement ($p < 0.01$) of Winsor Index in the patients **treated** with Picotamide vs placebo and a 15% increase of the photoplethysmographic wave amplitude in 11 (47.8%) patients. A statistically significant decrease ($p < 0.01$) of fibrinogen levels was observed in patients **treated** with picotamide vs placebo. No vascular accidents were observed during **treatment** with picotamide. We observed no side effects, nor untoward effects.

1990

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Set     Items   Description
S1     100172   CAMP
S2      32885   S1 AND HUMAN?
S3        454   S2 AND ADMINISTER?
S4          0   S3 AND PHARMACEUTICAL?
S5         63   S3 AND ANTAGONIST?
S6         51   RD (unique items)
S7          1   S6 AND IMMUNO?
S8         21   S6 AND TREAT?
S9          1   RP-8-BR-CAMPS
? s s6 not s8
              51  S6
              21  S8
     S10      30  S6 NOT S8
? t s10/3,ab/all

 10/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13450715   22105376   PMID: 12110614
   The highly selective CRF(2) receptor antagonist K41498 binds to
presynaptic CRF(2) receptors in rat brain.
  Lawrence A J; Krstew E V; Dautzenberg F M; Ruhmann A
  Department of Pharmacology, Monash University, Clayton VIC 3800,
Australia. Andrew.Lawrence@med.monash.edu.au
  British journal of pharmacology (England)  Jul 2002,  136 (6) p896-904
,  ISSN 0007-1188  Journal Code: 7502536
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  1. Novel analogues of antisauvagine-30 (aSvg-30), a selective
antagonist for CRF(2) receptors, have been synthesized and
characterized in vitro and in vivo. 2. The analogues were tested for their
ability to compete for [(125)I-Tyr(0)]Svg binding and to inhibit
Svg-stimulated adenylate cyclase activity in human embryonic kidney
(HEK) 293 cells, permanently transfected with cDNA coding for the
human CRF(1) (hCRF(1)), hCRF(2alpha) and hCRF(2beta) receptor. One
analogue [D-Phe(11), His(12), Nle(17)]Svg(11-40), named K41498, showed high
affinity binding to hCRF(2alpha) (K(i)=0.66+/-0.03 nM) and hCRF(2beta)
(K(i)=0.62+/-0.01 nM) but not the hCRF(1) receptor (k(i)=425+50 nM) and
decreased Svg-stimulated cAMP accumulation in hCRF(2) expressing
cells. In conscious Wistar-Kyoto rats, K41498 (1.84 microg, i.v.)
antagonized the hypotensive response to systemic urocortin (1.4 microg,
i.v.), but did not block the pressor response to centrally
administered urocortin (2.35 microg, i.c.v.). 3. K41498 was
subsequently radio-iodinated, and in autoradiographic studies, specific
(sensitive to rat urocortin, astressin and aSvg30, but insensitive to
antalarmin) binding of (125)I-K41498 (100 pM) was detected in the heart and
in selected brain regions including the nucleus tractus solitarius (NTS),
spinal trigeminal nucleus, lateral septum and around the anterior and
middle cerebral arteries. 4. Following unilateral nodose ganglionectomy,
binding of (125)I-K41498 was reduced by 65% in the ipsilateral NTS,
indicative of presynaptic CRF(2) receptors on vagal afferent terminals. 5.
These data demonstrate that K41498 is a useful tool to study native CRF(2)
receptors in the brain and periphery. British Journal of Pharmacology
(2002) 136, 896-904


 10/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13012998   21932110   PMID: 11935413
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Peptides interact in gonadotrophin regulation.
Evans J J
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Archives of physiology and biochemistry (Netherlands) Apr 2002, 110 (1-2) p154-61, ISSN 1381-3455 Journal Code: 9510153
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Main Citation Owner: NLM
Record type: In Process

The regulation of luteinizing hormone (LH) activity is vital to normal reproductive functioning of the female. Although gonadotrophin-releasing hormone (GnRH) has a prominent role in the regulation of LH it is now believed that other peptides are also involved. Among these peptides is oxytocin. The addition of oxytocin to cultures of pituitary cells from female rats elicited a concentration-dependent secretion of LH. This secretion was enhanced in an oestrogenised environment and was inhibited by progesterone and testosterone. Oxytocin **administered** to female rats at pro-oestrus advanced the endogenous LH surge that occurs on the evening of pro-oestrus. Conversely oxytocin receptor **antagonist** suppressed the production of the LH surge in a dose-dependent manner, indicating that endogenous oxytocin is a crucial component of LH regulation. In the **human** female, oxytocin **administered** during the late follicular phase advanced the onset of the midcycle LH surge. Oxytocin added to rat pituitary cells in vitro induced LH synthesis. Furthermore rats **administered** oxytocin on pro-oestrus had higher LH pituitary content following development of the LH surge than did rats **administered** saline. Thus oxytocin promoted synthesis and replacement in the pituitary of LH released into the circulation. Incubation of pituitary pieces with oxytocin plus GnRH induced secretion of amounts of LH greater than the sum of the amounts released by oxytocin and GnRH separately. Additionally the increased LH levels observed in the peripheral circulation of pentobarbitone-anaesthetised rats **administered** GnRH were enhanced if the rats received oxytocin prior to the GnRH. Thus oxytocin synergised with GnRH in stimulating LH release. Addition of diBucAMP reduced the oxytocin-mediated augmentation and dideoxyadenosine enhanced the augmentation, suggesting that oxytocin worked most efficiently in a milieu low in **cAMP** activity. The use of a cell immunoblot assay revealed that individual cells responded differently to oxytocin and to GnRH and that the two peptides could act on the same cell. Perifusion studies performed on hemipituitaries demonstrated that a LH response could be determined by the presence of three peptides, oxytocin, neuropeptide Y and GnRH. Hence oxytocin is potentially involved also in multiple interactions during the process of LH regulation. LH regulation is therefore apparently the result of a community of peptides acting in a co-operative network.

10/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12954086 21898559 PMID: 11900895
Assessment of the in vitro and in vivo biological activities of the **human** follicle-stimulating isohormones.
Barrios-De-Tomasi J; Timossi C; Merchant H; Quintanar A; Avalos J M; Andersen C Yding; Ulloa-Aguirre A
Research Unit in Reproductive Medicine, Hospital de Ginecobstetricia "Luis Castelazo Ayala", Instituto Mexicano del Seguro Social, Apdo. Postal No. 99-065, 10101 Unidad Independencia DF, Universidad Nacional Autonoma de Mexico, Mexico D.F., Mexico
Molecular and cellular endocrinology (Ireland) Jan 25 2002, 186 (2) p189-98, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: In Process

Gonadotropins are synthesized and released in different molecular forms. In this article, we present evidence that the glycosylation variants of **human** pituitary FSH exhibit differential and divergent effects at the target cell level and that less sialylated, short-lived variants may exert significant effects in in vivo conditions. Less acidic/sialylated glycoforms (elution pH value 6.60-4.60 as disclosed by high resolution chromatofocusing of anterior glycoprotein extracts), induced higher **cAMP** release, estrogen production and tissue-type plasminogen activator (tPA) enzyme activity as well as cytochrome P450 aromatase and tPA mRNA expression in cultured rat granulosa cells than the more acidic analogs (pH<4.76). By contrast, the more acidic/sialylated glycoforms induced higher alpha-inhibin subunit mRNA expression than their less acidic counterparts. In cumulus enclosed oocytes isolated from mice ovaries, addition of less acidic isoforms induced resumption of meiosis more efficiently than the more acidic analogs. Interestingly, the least acidic isoform (pH>7.10) behave as a strong **antagonist** of several FSH-mediated effects. Assessment of the in vivo effects of the isoforms on granulosa cell proliferation in follicles from immature rats, revealed that short-lived isoforms were equally or even more efficient than their more acidic counterparts in maintaining granulosa cell proliferation when **administered** immediately after hypophysectomy. These results show that the naturally occuring **human** FSH isoforms may exhibit differential or even unique effects at the target cell level and that factors other than the metabolic clearance rate of the molecule (including receptor-binding affinity and capability of the ligand to activate its receptor and trigger intracellular signaling) also play an important role in determining the net in vivo effects of a particular FSH variant.

10/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11336531 21396333 PMID: 11504812

Studies on mechanisms of low emetogenicity of YM976, a novel phosphodiesterase type 4 inhibitor.

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Journal of pharmacology and experimental therapeutics (United States) Sep 2001, 298 (3) p1142-9, ISSN 0022-3565 Journal Code: 0376362

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

YM976 is a novel and selective inhibitor of phosphodiesterase type 4 (PDE4) with a different chemical structure from rolipram. Orally **administered** YM976 showed anti-inflammatory activity (ED(50) = 2.8 mg/kg) similar to rolipram (3.5 mg/kg). On the other hand, the emetogenicity of YM976, one of the main adverse effects of PDE4 inhibitors, was lower (maximal non-emetic dose = 10 mg/kg) than that of rolipram (1 mg/kg). The reasons for this low emetogenicity of YM976 remain unclear, and the present study endeavored to elucidate the mechanisms. Candidates for the possible mechanisms included 1) PDE4 subtype selectivity, 2) binding affinity for HAR-conformation, and 3) brain penetration. YM976 exhibited affinity for high affinity for rolipram-conformation (HAR-conformation) (IC(50) = 2.6 nM) identical to that of rolipram (1.2 nM), and failed to show significant selectivity for the individual PDE4 subtype. These results suggested that neither subtype selectivity nor the affinity for HAR-conformation may be related to the low emetogenicity of YM976. YM976 showed a minor effect on reserpine-induced hypothermia, in contrast to rolipram. To estimate brain penetration, we then measured **cAMP** contents in peripheral tissues (peritoneal macrophages) and in the brain.

YM976 increased the **cAMP** content of peritoneal macrophages, but caused no significant increase in brain **cAMP** levels, while rolipram elevated the **cAMP** content of both tissues at the same dose. In conclusion, YM976 shows an apparent dissociation between its anti-inflammatory effects and emetogenicity, perhaps because of the poor brain penetration.

10/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11028658 21019673 PMID: 11138727
Activation of cerebral function by CS-932, a functionally selective M1 partial agonist: neurochemical characterization and pharmacological studies.
Iwata N; Kozuka M; Hara T; Kanek T; Tonohiro T; Sugimoto M; Niitsu Y; Kondo Y; Yamamoto T; Sakai J; Nagano M
Neuroscience and Immunology Research Laboratories, Sankyo Co., Ltd., Tokyo, Japan.
Japanese journal of pharmacology (Japan) Nov 2000, 84 (3) p266-80, ISSN 0021-5198 Journal Code: 2983305R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A newly synthesized agonist for muscarinic acetylcholine (ACh) receptors CS-932, (R)-3-(3-iso-xazoloxy)-1-azabicyclo-[2.2.2]octane hydrochloride, showed a relatively higher affinity for M1 than M2 receptors expressed in Chinese hamster ovary (CHO)-cells in comparison with ACh. CS-932 elevated the intracellular Ca2+ level only in M1-CHO cells, although ACh increased the level in both M1- and M3-CHO cells. CS-932 and ACh reduced forskolin-stimulated accumulation of **cAMP** in M2-CHO cells by 20% and 80%, respectively. This neurochemical profile of CS-932 indicates that the compound can activate M1-receptor-mediated functions selectively. CS-932 increased firing of cholinoceptive neurons in rat hippocampal slices, and this excitation was antagonized by pirenzepine, but not by AF-DX 116. CS-932 increased awake and decreased slow wave sleep episodes of daytime EEG in free-moving rats. It counteracted scopolamine-induced slow waves in rat cortical EEG. CS-932 also increased the power of alpha- and beta-waves, but decreased delta-wave of the cortical EEG in anesthetized monkeys. It ameliorated scopolamine-induced impairment of working memory in rats. Orally **administered** CS-932 had the best penetration into the brain among the muscarinic agonists tested and caused the least salivary secretion among the cholinomimetics examined. These results indicate that CS-932 has potential as a cognitive enhancer with fewer side effects in therapy for Alzheimer disease.

10/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10848610 20400267 PMID: 10940356
In vitro and in vivo pharmacological characterization of J-113397, a potent and selective non-peptidyl ORL1 receptor **antagonist**.
Ozaki S; Kawamoto H; Itoh Y; Miyaji M; Azuma T; Ichikawa D; Nambu H; Iguchi T; Iwasawa Y; Ohta H
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European journal of pharmacology (NETHERLANDS) Aug 18 2000, 402 (1-2) p45-53, ISSN 0014-2999 Journal Code: 1254354
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

1-[(3R,4R)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl -1, 3-dihydro-2H-benzimidazol-2-one (J-113397) was found to be the first potent nonpeptidyl ORL1 receptor **antagonist** (K(i): cloned **human** ORL1=1.8 nM) with high selectivity over other opioid receptors (K(i): 1000 nM for **human** mu-opioid receptor, >10,000 nM for **human** delta-opioid receptor, and 640 nM for **human** kappa-opioid receptor). In vitro, J-113397 inhibited nociceptin/orphanin FQ-stimulated [35S]guanosine 5'-O-(gamma-thio)triphosphate (GTP gamma S) binding to Chinese Hamster Ovary (CHO) cells expressing ORL1 (CHO-ORL1) with an IC(50) value of 5.3 nM but had no effect on [35S]GTP gamma S binding by itself. Schild plot analysis of the [35S]GTP gamma S binding assay and **cAMP** assay using CHO-ORL1 indicated competitive antagonism of J-113397 on the ORL1 receptor. In CHO cells expressing mu-, delta- or kappa-opioid receptors, J-113397 had no effects on [35S]GTP gamma S binding up to a concentration of 100 nM, indicating selective antagonism of the compound on the ORL1 receptor. In vivo, J-113397, when **administered** subcutaneously (s.c.), dose-dependently inhibited hyperalgesia elicited by intracerebroventricular (i.c.v.) administration of nociceptin/orphanin FQ in a tail-flick test with mice. An in vitro binding study using mouse brains indicated that J-113397 possesses high affinity for the mouse ORL1 receptor (K(i): 1.1 nM) as well as the **human** receptor. In summary, J-113397 is the first potent, selective ORL1 receptor **antagonist** that may be useful in elucidating the physiological roles of nociceptin/orphanin FQ.

10/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10307710 99308875 PMID: 10381145
Properties of native and in vitro glycosylated forms of the glucagon-like peptide-1 receptor **antagonist** exendin(9-39).
Meurer J A; Colca J R; Burton P S; Elhammer A P
Unit of Protein Research, Pharmacia & Upjohn, Kalamazoo, MI, USA.
Metabolism: clinical and experimental (UNITED STATES) Jun 1999, 48 (6) p716-24, ISSN 0026-0495 Journal Code: 0375267
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The intestinal hormone glucagon-like peptide-1-(7-36)-amide (GLP-1) has recently been implicated as a possible therapeutic agent for the management of type 2 non-insulin-dependent diabetes mellitus (NIDDM). However, a major difficulty with the delivery of peptide-based agents is their short plasma half-life, mainly due to rapid serum clearance and proteolytic degradation. Using a peptide analog of GLP-1, the GLP-1 receptor **antagonist** exendin(9-39), we investigated whether the conjugation of a carbohydrate structure to exendin(9-39) would generate a peptide with intact biological activity and improved survival in circulation. The C-terminal portion of exendin(9-39) was reengineered to generate an efficient site for enzymatic O-glycosylation. The modified exendin(9-39) peptide (exe-M) was glycosylated by recombinant UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1) alone or in conjunction with a recombinant GalNAc alpha2,6-sialyltransferase (Sialyl-T), resulting in exe-M peptides containing either the monosaccharide GalNAc or the disaccharide NeuAc alpha2,6GalNAc. The nonglycosylated and glycosylated forms of exe-M competed with nearly equal potency (> 90% of control) with the binding of [125I]GLP-1 to **human** GLP-1 receptors expressed on stably transfected COS-7 cells. In addition, each peptide was equally effective for inhibiting GLP-1-induced cyclic adenosine monophosphate (**cAMP**) production in vitro. Studies with rats demonstrated that the modified and glycosylated forms of exendin(9-39) could antagonize exogenously **administered** GLP-1 in vivo. Interestingly, glycosylated exendin(9-39) homologs were more than twice as effective as the nonglycosylated peptide for inhibiting

GLP-1-stimulated insulin production in vivo, suggesting a longer functional half-life in the circulation for glycosylated peptides. Results from in vivo studies with 3H-labeled peptides suggest that the glycosylated peptides may be less susceptible to modification in the circulation.

10/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10255665 99234420 PMID: 10213797
Recent advances with the CRF1 receptor: design of small molecule inhibitors, receptor subtypes and clinical indications.
McCarthy J R; Heinrichs S C; Grigoriadis D E
Neurocrine Biosciences, Inc., San Diego, CA 92121, USA. jmccarthy@neuroscience.com
Current pharmaceutical design (NETHERLANDS) May 1999, 5 (5) p289-315 , ISSN 1381-6128 Journal Code: 9602487
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Corticotropin-releasing factor (CRF) has been widely implicated as playing a major role in modulating the endocrine, autonomic, behavioral and immune responses to stress. The recent cloning of multiple receptors for CRF as well as the discovery of non-peptide receptor **antagonists** for CRF receptors have begun a new era of CRF study. Presently, there are five distinct targets for CRF with unique cDNA sequences, pharmacology and localization. These fall into three distinct classes, encoded by three different genes and have been termed the CRF1 and CRF2 receptors (belonging to the superfamily of G-protein coupled receptors) and the CRF-binding protein. The CRF2 receptor exists as three splice variants of the same gene and have been designated CRF2a CRF2b and CRF2g. The pharmacology and localization of all of these proteins in brain has been well established. The CRF1 receptor subtype is localized primarily to cortical and cerebellar regions while the CRF2a receptor is localized to subcortical regions including the lateral septum, and paraventricular and ventromedial nuclei of the hypothalamus. The CRF2b receptor is primarily localized to heart, skeletal muscle and in the brain, to cerebral arterioles and choroid plexus. The CRF2g receptor has most recently been identified in **human** amygdala. Expression of these receptors in mammalian cell lines has made possible the identification of non-peptide, high affinity, selective receptor **antagonists** . While the natural mammalian ligands oCRF and r/hCRF have high affinity for the CRF1 receptor subtype, they have lower affinity for the CRF2 receptor family making them ineffective labels for CRF2 receptors. [125I]Sauvagine has been characterized as a high affinity ligand for both the CRF1 and the CRF2 receptor subtypes and has been used in both radioligand binding and receptor autoradiographic studies as a tool to aid in the discovery of selective small molecule receptor **antagonists**. A number of non-peptide CRF1 receptor **antagonists** that can specifically and selectively block the CRF1 receptor subtype have recently been identified. Compounds such as CP 154,526 (12), NBI 27914 (129) and Antalarmin (154) inhibit CRF-stimulation of **cAMP** or CRF-stimulated ACTH release from cultured rat anterior pituitary cells. Furthermore, when **administered** peripherally, these compounds compete for ex vivo [125I]sauvagine binding to CRF1 receptors in brain sections demonstrating their ability to cross the blood-brain-barrier. In in vivo studies, peripheral administration of these compounds attenuate stress-induced elevations in plasma ACTH levels in rats demonstrating that CRF1 receptors can be blocked in the periphery. Furthermore, peripherally **administered** CRF1 receptor **antagonists** have also been demonstrated to inhibit CRF-induced seizure activity. These data clearly demonstrate that non-peptide CRF1 receptor **antagonists**, when **administered** systemically, can specifically block central CRF1 receptors and provide tools that can be used to determine the role of CRF1

receptors in various neuropsychiatric and neurodegenerative disorders. In addition, these molecules will prove useful in the discovery and development of potential orally active therapeutics for these disorders.

10/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10045620 99020670 PMID: 9803829
A possible molecular basis for the effect of gastric anti-ulcerogenic drugs.
Balint G A
Department of Psychiatry, Albert Szent-Gyorgyi Medical University, Szeged, Hungary.
Trends in pharmacological sciences (ENGLAND) Oct 1998, 19 (10) p401-3, ISSN 0165-6147 Journal Code: 7906158
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The exact mechanism of action of the anti-ulcerogenic drugs is still under debate. According to the literature, under normal conditions the **cAMP** :cGMP ratio in the rat gastric mucosa is approximately 8:10. Following prostacyclin administration, this ratio transiently decreases but later shows a strong elevation, indicating profound changes in the intracellular cyclic nucleotide balance. There is evidence that this elevation or 'shift' in the **cAMP**:cGMP ratio is linked, on a cellular or molecular level, to the anti-ulcerogenic, cytoprotective processes in the stomach. Cimetidine and ranitidine (widely used H2 receptor-blocking drugs) **administered** at doses that are too low to interfere with gastric acid secretion, cause an elevation in the **cAMP**:cGMP ratio, an effect that is also observed with other prostaglandin derivatives and anti-ulcerogenic drugs. In this article, Gabor A. Balint discusses these data and how the elevation of the gastric mucosal **cAMP**:cGMP ratio is a useful molecular marker that could provide insights into the effects of anti-ulcerogenic drugs.

10/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09974836 98422149 PMID: 9751529
A C-terminal fragment of Agouti-related protein increases feeding and antagonizes the effect of alpha-melanocyte stimulating hormone in vivo.
Rossi M; Kim M S; Morgan D G; Small C J; Edwards C M; Sunter D; Abusnana S; Goldstone A P; Russell S H; Stanley S A; Smith D M; Yagaloff K; Ghatei M A; Bloom S R
Endocrine Unit, Imperial College School of Medicine, Hammersmith Hospital, London, UK.
Endocrinology (UNITED STATES) Oct 1998, 139 (10) p4428-31, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Agouti-related protein (Agrp) is present in rat and **human** hypothalamus and is structurally related to agouti protein. Overexpression of either of these proteins results in obesity. However the effect of exogenous Agrp and its in vivo interaction with alpha-melanocyte stimulating hormone (alphaMSH), the likely endogenous melanocortin 3 and 4 receptor (MC3-R and MC4-R) agonist, have not been demonstrated. We report that 1 nmol of Agrp(83-132), a C-terminal fragment of Agrp, when **administered** intracerebroventricularly (ICV) into rats, increased food intake over a 24-h period (23.0+/-1.4 g saline vs 32.9+/-2.3 g Agrp,

p<0.05). The hyperphagia was similar to that seen when 1 nmol of the synthetic MC3-R and MC4-R **antagonist** SHU9119 was given i.c.v. (19.6+/-1.8 g saline vs 32.5+/-1.7 g SHU9119, p<0.001). Both Agrp(83-132) and SHU9119 blocked the reduction in 1-h food intake of i.c.v. alphaMSH at the beginning of the dark phase. This effect occurred independently of whether the **antagonists** were **administered** simultaneously, or nine hours prior, to the alphaMSH. We have also shown Agrp(83-132) is an **antagonist** at the MC3-R and MC4-R, with similar inhibition of **cAMP** activation to that previously reported for the full length peptide. In conclusion, Agrp(83-132) **administered** i.c.v. increases feeding with long lasting effects and is able to inhibit the action of alphaMSH. This interaction may be mediated by the MC3-R and/or MC4-R.

10/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09813153 98240486 PMID: 9579323
Dopamine D1-like receptors and reward-related incentive learning.
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Department of Psychology, Queen's University, Kingston, Canada. beninger@pavlov.psyc.queensu.ca
Neuroscience and biobehavioral reviews (UNITED STATES) Mar 1998, 22 (2) p335-45, ISSN 0149-7634 Journal Code: 7806090
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

There now is general agreement that dopaminergic neurons projecting from ventral mesencephalic nuclei to forebrain targets play a critical role in reward-related incentive learning. Many recent experiments evaluate the role of dopamine (DA) receptor subtypes in various paradigms involving this type of learning. The first part of this paper reviews evidence from these studies that use **antagonists** or agonists relatively specific for D1- or D2-like receptors in operant paradigms with food, brain stimulation, self-**administered** stimulant or conditioned rewards or place conditioning. The focus is on studies that directly compare agents acting at the two DA receptor families, especially those studies where the agents produce differential actions. Results support the conclusion that D1-like receptors play a more critical role in reward-related learning than D2-like receptors. D1-like receptors initiate a cascade of intracellular events including cyclic adenosine monophosphate (**cAMP**) formation and activation of **cAMP**-dependent protein kinase (PKA). The final section of this paper reviews evidence from a wide range of neuroscience experiments that implicates the **cAMP** /PKA pathway in learning in general and in reward-related incentive learning in particular. We conclude that the molecular mechanism underlying DA-mediated incentive learning may involve DA release in association with reward, stimulation of D1-like receptors, activation of the **cAMP** /PKA cascade and additional intracellular events leading to modification of cortico-striatal glutamatergic synapses activated by stimuli encountered in close temporal contiguity with reward. Thus, when reward-related incentive learning takes place, it may be the action of DA acting at D1-like receptors that leads to plastic changes in the striatum that form the substrate of that learning.

10/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09575523 97467008 PMID: 9328348
Derivation of functional **antagonists** using N-terminal extracellular domain of gonadotropin and thyrotropin receptors.
Osuga Y; Kudo M; Kaipia A; Kobilka B; Hsueh A J
Department of Gynecology and Obstetrics, Stanford University Medical

School, California 94305, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Oct 1997, 11 (11) p1659-68, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: HD-23273; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Receptors for the glycoprotein hormones, LH/CG, FSH, and TSH, are a unique subclass of the seven-transmembrane, G protein-coupled proteins with a large N-terminal extracellular (ecto-) domain. Although ecto-domains of gonadotropin receptors confer ligand binding, expression of soluble binding proteins has been difficult. We fused the ecto-domains of LH or FSH receptors to the single-transmembrane domain of CD8 and found that hybrid proteins anchored on the cell surface retained high-affinity ligand binding. Inclusion of a junctional thrombin cleavage site in the hybrids allowed generation of soluble receptor fragments that interfered with gonadotropin binding to their receptors and blocked **cAMP** production stimulated by gonadotropins. Cross-linking analyses confirmed the formation of high molecular weight complexes between receptor ecto-domains and their specific ligands. A similar approach also generated a soluble TSH receptor fragment capable of blocking TSH-induced signal transduction. When **administered** to rats, the soluble FSH receptor fragment retarded testis growth and induced testis cell apoptosis. These findings demonstrate the feasibility of generating ligand-binding regions of glycoprotein hormone receptors to selectively neutralize actions of gonadotropins and TSH, thus allowing future design of novel contraceptives and management of different gonadal and thyroid dysfunction. The present study represents the first successful derivation of soluble, ligand-binding domains from glycoprotein hormone receptors as functional **antagonists**. Similar approaches could allow generation of ecto-domains of related receptors to neutralize actions of ligands or receptor antibodies and to facilitate structural-functional analysis.

10/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08841510 96198780 PMID: 8612519
Calcitonin is a physiological inhibitor of prolactin secretion in ovariectomized female rats.
Shah G V; Pedchenko V; Stanley S; Li Z; Samson W K
Department of Surgery, University of Kansas Medical Center, Kansas City 66160, USA.
Endocrinology (UNITED STATES) May 1996, 137 (5) p1814-22, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK-45044; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Calcitonin (CT) inhibits secretion of PRL when **administered** intravenously in rats and **humans**. It also inhibits PRL release from cultured rat anterior pituitary (AP) cells. Recent evidence suggests that CT-like immunoreactive peptide is synthesized and released from the AP gland. However, its physiological role in the regulation of PRL secretion has not been understood. Present studies tested the role of endogenous pituitary CT (pit-CT) in the regulation of PRL secretion in vivo by passive immunization. In the first group of experiments, ovariectomized (ovx) adult female rats were **administered** either preimmune or anti-salmon CT (sCT) serum, and their serum PRL levels were analyzed at various time points up to 3 h. A second group of experiments examined the effects of anti-sCT serum and dopamine on PRL release from cultured rate AP cells. In the next group of experiments, the regional distribution of pit-CT

secretion was examined in different sections of the AP gland. In the last set, CT-like activity of AP extract was tested in neonatal rat kidney cells, which respond to CT with an increase in **cAMP** accumulation. These experiments also tested whether anti-sCT serum reduces AP extract-induced increase in **cAMP** accumulation. The results suggest that anti-sCT serum dramatically increased serum PRL levels (by 5-fold) of ovx rats within 30 min of administration. The serum PRL levels declined gradually after the peak. However, a significant increase in serum PRL levels was maintained by the anti-sCT serum for the duration of the experiment. The anti-serum also induced a significant increase in PRL release from cultured AP cells when added to the presence or absence of dopamine. The distribution profile of pit-CT within the AP gland suggests that the release of pit-CT immunoreactivity was significantly greater in the inner sections, and anti-sCT serum also caused greater increase in PRL release in these sections. Finally, AP extract and sCT stimulated **cAMP** accumulation in neonatal rat kidney cells, and anti-sCT serum significantly reduced AP extract-induced **cAMP** accumulation. These results demonstrate that pit-CT is an important regulator of tonic PRL secretion in female rats and can potently inhibit PRL secretion even in the presence of dopamine.

10/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08681427 96053774 PMID: 7549226
Pharmacological modulation of platelet-derived growth factor (B) mRNA expression in alveolar macrophages and adherent monocytes.
Kotecha S; Taylor I K; Shaw R J
Department of Respiratory Medicine, St Mary's Hospital Medical School, London, UK.
Pulmonary pharmacology (ENGLAND) Dec 1994, 7 (6) p383-91, ISSN 0952-0600 Journal Code: 9007551
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The macrophage profibrotic cytokine, Platelet Derived Growth Factor B [PDGF(B)], is thought to play a central role in orchestrating the fibrotic response in the pathogenesis of cryptogenic fibrosing alveolitis. In this study, we have asked if drugs that increase intracellular **cAMP** and are commonly **administered** to patients with lung disease have the ability to downregulate PDGF(B) mRNA. Incubation of **human** alveolar macrophages from healthy smokers in the presence of dibutyryl **cAMP** prevented the previously reported dexamethasone-induced increase in PDGF(B) mRNA ($P < 0.05$). Similarly, the combination of aminophylline (2.5 mM) and salbutamol (1 microM) prevented the adherence-dependent increase in PDGF(B) mRNA in adherent **human** peripheral blood monocytes ($P < 0.05$), whilst causing an increase in the mRNA expression of the **cAMP**-dependent gene c-fos ($P = 0.059$), and an increase in the intracellular concentration of **cAMP** ($P = 0.05$). Finally, the presence of a lower concentration of aminophylline (0.25 m) in conjunction with salbutamol (1 microM) also prevented the dexamethasone-induced increase in PDGF(B) mRNA in alveolar macrophages from healthy smokers ($P < 0.05$). Stimulation by these drugs was not associated with a change in the abundance of the mRNA of the house-keeping gene, glyceraldehyde-3-phosphate dehydrogenase. We speculate that drugs, which increase intracellular **cAMP**, may provide a novel therapeutic avenue whereby PDGF(B) expression in patients with cryptogenic fibrosing alveolitis may be reduced.

10/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08678875 96007889 PMID: 8562311
Role of tyrosine kinase in insulin release in an insulin secreting cell line (INS-1).
Verspohl E J; Tollkuhn B; Kloss H
Department of Pharmacology, University of Muenster, Germany.
Cellular signalling (ENGLAND) Jul 1995, 7 (5) p505-12, ISSN 0898-6568 Journal Code: 8904683
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tyrosine kinases are involved in cell signalling of growth factors such as insulin and insulin-like growth factor (IGF-I) and others. Insulin and IGF-I receptors which possibly feedback on insulin release are established in insulin-secreting cells. The role of tyrosine kinase in insulin secretion is controversial. Both the tyrosine kinase inhibitors tyrphostin 25 (TYR) and genistein (GEN), but not its structurally similar albeit biologically inactive analogue daidzein, increase insulin release at 16.7 mM glucose in INS-1 cells, an insulin secreting cell line. Tyrosine kinase activity is inhibited by GEN, but not diadzein. The inhibitory effects of either insulin or IGF-I on insulin release are abolished by 10(-4) M GEN but not by daidzein indicating an involvement of tyrosine kinase in the inhibitory effect of both insulin and IGF-I on insulin release. Since GEN was argued not to be specific for tyrosine kinase, several second messengers were investigated. **cAMP** is not influenced. The insulinotropic effect of acutely **administered** TPA is not influenced by GEN while in protein kinase C (PKC)-downregulated cells the insulinotropic effect of GEN is preserved: both indicate no involvement of PKC in GEN effect. Since pertussis toxin (PT) pretreatment has no effect on the inhibitory effects of IGF-I on insulin release, a PT-sensitive G-protein is not likely to be involved. The data indicate that tyrosine kinase is involved in the inhibitory effects of insulin and IGF on insulin release in INS-1 cells, possibly mediating the negative feedback effect.

10/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08257808 95015021 PMID: 7929829
Adenosine-mediated inhibition of platelet aggregation by acadesine. A novel antithrombotic mechanism in vitro and in vivo.
Bullough D A; Zhang C; Montag A; Mullane K M; Young M A
Department of Cardiovascular Pharmacology, Gensia Inc., San Diego, California 92121.
Journal of clinical investigation (UNITED STATES) Oct 1994, 94 (4) p1524-32, ISSN 0021-9738 Journal Code: 7802877
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Inhibition of platelet aggregation by acadesine was evaluated both in vitro and ex vivo in **human** whole blood using impedance aggregometry, as well as in vivo in a canine model of platelet-dependent cyclic coronary flow reductions. In vitro, incubation of acadesine in whole blood inhibited ADP-induced platelet aggregation by 50% at 240 +/- 60 microM. Inhibition of platelet aggregation was time dependent and was prevented by the adenosine kinase inhibitor, 5'-deoxy 5-iodotubercidin, which blocked conversion of acadesine to its 5'-monophosphate, ZMP, and by adenosine deaminase. Acadesine elevated platelet **cAMP** in whole blood, which was also prevented by adenosine deaminase. In contrast, acadesine had no effect on ADP-induced platelet aggregation or platelet **cAMP** levels in platelet-rich plasma, but inhibition of aggregation was restored when isolated erythrocytes were incubated with acadesine before reconstitution with platelet-rich plasma. Acadesine (100 mg/kg i.v.) **administered** to

human subjects also inhibited platelet aggregation ex vivo in whole blood. In the canine Folts model of platelet thrombosis, acadesine (0.5 mg/kg per min, i.v.) abolished coronary flow reductions, and this activity was prevented by pretreatment with the adenosine receptor **antagonist**, 8-sulphophenyltheophylline. These results demonstrate that acadesine exhibits antiplatelet activity in vitro, ex vivo, and in vivo through an adenosine-dependent mechanism. Moreover, the in vitro studies indicate that inhibition of platelet aggregation requires the presence of erythrocytes and metabolism of acadesine to acadesine monophosphate (ZMP).

10/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07641079 93162725 PMID: 8381769
cAMP -specific phosphodiesterase inhibitor, rolipram, reduces eosinophil infiltration evoked by leukotrienes or by histamine in guinea pig conjunctiva.
Newsholme S J; Schwartz L
Department of Toxicology SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406.
Inflammation (UNITED STATES) Feb 1993, 17 (1) p25-31, ISSN 0360-3997 Journal Code: 7600105
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effect of rolipram, an isozyme IV-selective inhibitor of **cAMP** -specific phosphodiesterase, was evaluated in a guinea pig eye model of tissue eosinophilia. (R)-rolipram was **administered** by gavage to guinea pigs 1 h prior to topical ocular challenge with a mixture of leukotrienes (LTs) (10 ng LTB4 + 1000 ng LTD4/eye) or with histamine dihydrochloride (1 mg/eye). Conjunctivae were evaluated histologically 6 h after challenge. Eosinophil counts per millimeter of conjunctival epithelium in LT-challenged animals that received (R)-rolipram at dosages of 0.1, 0.3, 1, 3, or 10 mg/kg were reduced by 63, 63, 84, 81 and 90% respectively, compared to LT-challenged controls. Reduction was statistically significant ($P < 0.05$) at all dosages. Eosinophil counts per millimeter of epithelium in histamine-challenged animals that received 10 mg/kg (R)-rolipram were reduced by 79% compared to histamine-challenged controls ($P < 0.01$). The results indicate that (R)-rolipram inhibits the response to two distinct classes of mediator in this model of eosinophil infiltration, adding support to the contention that isozyme IV-selective **cAMP** phosphodiesterase inhibitors offer therapeutic potential for **human** asthma.

10/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07578886 93106075 PMID: 1468513
Antagonists of the **human** TSH receptor: in vitro and in vivo studies of their functional and immunological effects.
Hoermann R; Schumm-Draeger P M; Mann K
Medical Department II, Klinikum Grosshadern, University of Munich, Germany.
Experimental and clinical endocrinology (GERMANY) 1992, 100 (1-2) p36-40, ISSN 0232-7384 Journal Code: 8302802
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have developed and characterized a prototype of a TSH receptor **antagonist** derived from the hCG molecule. This may be used to block

human TSH receptor both functionally and immunologically, particularly in the study of Graves' disease. Our hCG derived TSH receptor blocker compares favorably with other substances (e.g. deglycosylated forms of TSH, synthetic peptides of the alpha or beta subunit of TSH) that hare been reported to inhibit bTSH binding or bTSH-stimulated **cAMP** response (Joshi et al., 1981; Morris et al., 1988). It has a much higher affinity for **human** TSH receptor than the TSH subunit peptides and it is the only substance an efficacy of which has been proven in vivo so far. Recent progress in the synthesis of recombinant glycoprotein hormones should permit to biosynthetically produce this or a similar TSH receptor **antagonist** . With respect to Graves' disease, the data suggest that TSH receptor, in addition to its role in maintaining thyroid hyperfunction, plays also a role in propagating the thyroid autoimmune disease itself. Stimulation of TSH receptor by bTSH as well as TSAb enhances the expression of HLA class II antigens on the surface of thyrocytes, and a blockade of TSH receptor results in a substantial inhibition of this immunological key event. This could possibly explain why suppression of TSH by **administering** levothyroxine was found in a recent study by Hashizume and coworkers (1991) to decrease TSAb titers and to reduce relapse rate in patients with Graves' hyperthyroidism.(ABSTRACT TRUNCATED AT 250 WORDS)

10/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07456027 92390183 PMID: 1518664
Effect of H2-blockers, cimetidine and famotidine, on histamine nasal provocative test.
Ogino S; Irifune M; Harada T; Matsunaga T
Department of Otolaryngology, Osaka University Medical School, Japan.
ORL; journal for oto-rhino-laryngology and its related specialties (SWITZERLAND) 1992, 54 (3) p152-4, ISSN 0301-1569 Journal Code: 0334721
Document type: Clinical Trial; Controlled Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The H2-receptor is considered to mediate the stabilization of the membrane of mast cells by enhancing **cAMP** synthesis. In the present study, we investigated the effect of H2-receptor **antagonists**, i.e. H2-blockers, on nasal hypersensitivity using a histamine nasal provocative test. A 7-day administration of cimetidine tended to lower the histamine threshold. Famotidine **administered** in the same way caused no significant decrease in the histamine threshold. Based on the above results, we postulate that famotidine should be preferred to cimetidine as an H2-blocker in patients with gastric and/or duodenal ulcers.

10/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07252549 92181908 PMID: 1311946
Inhibition of cyclic AMP- and cyclic GMP-mediated dilations in isolated arteries by oxidized low density lipoproteins.
Galle J; Bauersachs J; Busse R; Bassenge E
Department of Applied Physiology, University of Freiburg, FRG.
Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association (UNITED STATES) Feb 1992, 12 (2) p180-6, ISSN 1049-8834 Journal Code: 9101388
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We studied the effects of native (N) and oxidized (Ox) low density

lipoproteins (LDLs) on adenosine 3',5'-cyclic monophosphate (**cAMP**)-mediated and on guanosine 3',5'-cyclic monophosphate (cGMP)-mediated dilator mechanisms in isolated, perfused **human** mammary and rabbit femoral arteries. Dilations were induced in preconstricted, deendothelialized segments by either forskolin (Fo) or sodium nitroprusside (SNP) (intraluminal or adventitial application). Lipoproteins (0.5 mg/ml) were **administered** to the segments from the intraluminal side. N-LDL had no effect on Fo-induced dilation and caused a weak attenuation of SNP-induced dilation only when SNP was also **administered** into the intraluminal perfusate. In contrast, Ox-LDL inhibited both Fo- and SNP-induced dilation, independent of the route of dilator application. The effects of Ox-LDL were specific for dilation mediated by cyclic nucleotides. Dilation elicited by the Ca2+ **antagonist** nitrendipine was inhibited neither by N-LDL nor by Ox-LDL. Determination of basal and stimulated (SNP, Fo) cGMP and **cAMP** content in rabbit femoral segments after preincubation with N-LDL and Ox-LDL revealed a significant decrease of stimulated vascular cGMP and **cAMP** content by Ox-LDL, whereas N-LDL had no effect. These data indicate that Ox-LDL selectively inhibits vascular smooth muscle relaxation elicited by increases in cyclic nucleotides. This inhibition might contribute to the attenuation of vasodilation in hypercholesterolemia and atherosclerosis.

10/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07248360 92172445 PMID: 1347224
Amiloride antagonizes beta-adrenergic stimulation of **cAMP** synthesis and Cl- secretion in **human** tracheal epithelial cells.
Davis P B; Silski C L; Liedtke C M
Department of Pediatrics, Case Western Reserve University at Rainbow Babies and Childrens Hospital, Cleveland, Ohio 44106.
American journal of respiratory cell and molecular biology (UNITED STATES) Feb 1992, 6 (2) p140-5, ISSN 1044-1549 Journal Code: 8917225
Contract/Grant No.: DK-27651; DK; NIDDK; HL-28386; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Amiloride, a potent blocker of the sodium channel in airway epithelium, has been **administered** by aerosol as a therapeutic agent for cystic fibrosis. Because amiloride in high concentration has been reported to interfere with cell functions, including adrenergic responses, we tested the ability of amiloride to inhibit beta-adrenergic responses in **human** tracheal epithelial cells. Amiloride (10(-4) M), applied from the basolateral surface of a cell monolayer, inhibited the changes in transepithelial potential and short circuit current to isoproterenol (10(-6) M). The stimulation of cyclic adenosine monophosphate (**cAMP**) synthesis by isoproterenol was inhibited in dose-dependent fashion by amiloride (P = 0.007 by multivariate ANOVA with multiple samples correction). Amiloride did not affect baseline transepithelial potential, short circuit current, basal **cAMP** levels, **cAMP** response to prostaglandin E2, or basal adenylate cyclase activity measured directly in membrane preparations. Therefore, it is unlikely that amiloride exerts a nonspecific toxic effect on adenylate cyclase, receptor-cyclase coupling, or substrate or cofactor supply. The binding of [125I]iodocyanopindolol (ICYP), a beta-adrenergic receptor **antagonist**, to membranes from **human** tracheal epithelial cells could be displaced by amiloride with IC50 = 410 microM; displacement was 70% at 10(-3) M amiloride. These data are most consistent with the hypothesis that amiloride inhibits beta-adrenergic responses in airway epithelial cells by occupying beta-adrenergic receptor sites. Therapeutic administration of amiloride should take into account its affinity for adrenergic receptors.

10/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06629382 90329759 PMID: 2142911
[Picotamide: prevention and therapy of diabetic vasculopathies. A double-blind clinical study]
Picotamide: prevenzione e terapia della vasculopatia diabetica. Esperienza clinica in doppio cieco.
Pibiri L; Petruzzo P; De Giudici A; Brotzu G
Istituto di Patologia e Chirurgia, Universita degli Studi di Cagliari.
La Clinica terapeutica (ITALY) May 31 1990, 133 (4) p233-7, ISSN 0009-9074 Journal Code: 0372604
Document type: Clinical Trial; Controlled Clinical Trial; Journal Article ; English Abstract
Languages: ITALIAN
Main Citation Owner: NLM
Record type: Completed
Picotamide is the most interesting compound of 4-OH isophthalic acid. It is effective in vitro and in vivo. Picotamide induces inhibition of platelet aggregation: it is a thromboxane synthetase inhibitor and a thromboxane receptor **antagonist** . Picotamide causes cyclic endoperoxide accumulation and diverts their metabolism toward PgI2 synthesis in endothelial cells. PGI2 stimulates the adenylate cyclase with **cAMP** synthesis which makes platelets less sensitive to aggregatory stimulation. Picotamide induces enhancement of fibrinolytic activity, with significant reduction in the level of circulating plasminogen but in the same time it does not affect antithrombin III and FDP levels. In the present study picotamide or placebo were **administered** in a double blind trial at 600 mg daily for six months to 51 patients effected by diabetic macro and/or microangiopathy. The patients were 38 men and 13 women, the age was between 20 and 80 years (mean age 62.34). Twenty-seven patients were affected by type I diabetes and 24 by type II diabetes. Twenty-three of these patients presented macro-angiopathic lesions, 9 only microangiopathic lesions and 13 both. Twenty-five patients received picotamide and the other 25 an identical placebo for six months. One patient manifested myocardial infarction during the wash-out period and failed to enter the study. The following determinations were carried out: at T0 clinical examination, Doppler ultrasonography, Winsor Index, laboratory parameters; after 90 days (T90) clinical examination and Winsor Index and after 180 days (T180) were repeated photoplethysmography and clinical parameters too. Patients were not only evaluated for the vascular disease of lower extremities, but also for the other complications of diabetes, as retinopathy, nephropathy, cardiac and cerebrovascular disease.(ABSTRACT TRUNCATED AT 250 WORDS)

10/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06542644 90236370 PMID: 2561360
[The role of gonadotropins, cyclic AMP, 22-R-OH-cholesterol and cofactors in regulating endocrine functions of the Leydig cells in rats. III. Mechanisms responsible for "desensitization" of the Leydig cells of rats caused by high doses of hCG]
Rola gonadotropin, **cAMP** , 22-R-OH-cholesterolu i kofaktorow w regulacji funkcji endokrynnej komorek Leydiga u szczura. III. Proba wyjasnienia mechanizmow odpowiedzialnych za "desensybilizacje" szczurzych komorek Leydiga, wywolana wysokimi dawkami hCG.
Grochowski D; Szamatowicz M
Ginekologia polska (POLAND) May 1989, 60 (5) p252-60, ISSN 0017-0011 Journal Code: 0374641
Document type: Journal Article ; English Abstract
Languages: POLISH

Main Citation Owner: NLM
Record type: Completed
Two groups of rats (a control group and the group examined) were **administered** intraperitoneally supraphysiological doses of hCG in order to induce a "down regulation" effect on the level of receptors LH and to achieve the desensibilization of Leydig cells. The authors tried to find out at which stage of sequence of changes from receptor stimulation to hormone production there appears a state of cellular resistance to further stimulation. Sections of the nucleus were incubated with various substances influencing steridogenesis (LH, hCG, dbcAMP, 22-R-OH-cholesterol, NAD + NADP + G-6-P + G-6-PDH). An index of the influence of the above substances on the synthesis of androgens were amounts of pregnenolon as the first and testosterone as the final stage of hormonal changes marked radioimmunologically in nucleus homogenates and incubating media. It was shown that the resistance of Leydig cells to further stimulation in the group of animals that were given high doses of hCG is the result of enzymatic blocks in testosterone synthesis. The first block is "late" block of 17 alpha-hydroxylase and 17-20 desmolase, disturbing transforming of 21-carbon steriods into 19-carbon androgens. When the dose of hCG increases, there appears the second block, the so called "early" block, disturbing mitochondrial synthesis of pregnenolon. It was found that exogenic cofactors are in a position, at least partially, to restore the activity of blocked enzymes.(ABSTRACT TRUNCATED AT 250 WORDS)

10/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06057974 89139813 PMID: 2537341
Characterization of a monoclonal antibody which inhibits the biological activity of **human** chorionic gonadotrophin in **human** corpora lutea.
Hahlin M; Lindblom B; Schuurs A; Kloosterboer H; Hamberger L
Department of Obstetrics and Gynaecology, University of Goteborg, Sweden.
Human reproduction (Oxford, England) (ENGLAND) Feb 1989, 4 (2) p152-7, ISSN 0268-1161 Journal Code: 8701199
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In the present study a murine monoclonal antibody (MCA), directed against **human** chorionic gonadotrophin (HCG), was investigated in vitro utilizing **human** corpora lutea (CL). The CL were excised from women of fertile age undergoing various gynaecological operations. The CL specimens were cut into pieces and incubated in standard medium for 2 or 4 h in the presence of HCG, luteinizing hormone (HLH) or prostaglandin (PG) E2 alone or in combination with the MCA directed against HCG. After incubation, the tissue levels of cyclic adenosine 3',5' monophosphate (**cAMP**) and the media contents of progesterone (P) were determined. HCG, HLH and PGE2 stimulated both **cAMP** and P formation in CL of all ages, while the MCA alone had no effect on these parameters. The MCA, however, effectively counteracted the stimulatory effect of HCG on both **cAMP** and P formation on a 1:1 molar basis. This **antagonistic** effect was clearly reversible and could be overcome by increasing the HCG concentrations. The stimulatory effect of HLH and PGE2, on the other hand, was not influenced by the antibody, even when **administered** at high concentrations. These in-vitro data show that the MCA studied effectively counteracts the stimulatory effect of HCG on **human** luteal tissue with high specificity.

10/3,AB/25 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13545563 BIOSIS NO.: 200200174384
beta-adrenergic desensitization after burn excision not affected by the use of epinephrine to limit blood loss.
AUTHOR: McQuitty Christopher K(a); Berman Jeffrey; Cortiella Joaquin; Herndon David; Mathru Mali
AUTHOR ADDRESS: (a)Department of Anesthesiology, University of Texas Medical Branch, Suite 2A John Sealy, Galveston, TX, 77555-0591**USA E-Mail: cmcquitt@utmb.edu
JOURNAL: Anesthesiology (Hagerstown) 93 (2):p351-358 August, 2000
MEDIUM: print
ISSN: 0003-3022
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Burn patients have impaired myocardial function and decreased beta-adrenergic responsiveness. Further beta-adrenergic dysfunction from systemic absorption of topically **administered** epinephrine that is given to limit blood loss during burn excision could affect perioperative management. The authors evaluated the effect of topical epinephrine administration to patients during burn excision on the lymphocytic beta-adrenergic response. Methods: Fifty-five patients (age, 2-18 yr) with 20-90% body surface area burns received a standardized anesthetic for a burn excision procedure. Lymphocyte samples were taken at baseline and 1 and 3 h after the initial use of epinephrine (n = 43) or thrombin (controls, n = 12). Plasma epinephrine levels were measured by high-performance liquid chromatography. Lymphocyte beta-adrenergic responsiveness was assessed by measuring production of cyclic adenosine monophosphate (**cAMP**) after stimulation with isoproterenol, prostaglandin E1 (PGE1), and forskolin. beta-adrenergic receptor binding assays using iodopindolol and CGP12177 yielded beta-adrenergic receptor density. Results: Epinephrine levels were elevated at 1 h ($P < 0.01$) and 3 h ($P < 0.01$) after epinephrine use but not in control patients. Production of **cAMP** in lymphocytes 1 h after epinephrine was greater in patients receiving epinephrine than in control patients on stimulation with isoproterenol ($P < 0.05$) and PGE1 ($P < 0.05$). Three hours after epinephrine administration, production of **cAMP** decreased when compared with baseline in both control patients and those receiving epinephrine after stimulation with isoproterenol ($P < 0.05$), PGE1 ($P < 0.05$), and forskolin ($P < 0.05$). Lymphocytic beta-adrenergic receptor content was not changed. Conclusions: Topical epinephrine to limit blood loss during burn excision resulted in significant systemic absorption and increased plasma epinephrine levels. Acute sensitization of the lymphocytic beta-adrenergic cascade was induced by the administration of epinephrine reflected by increased **cAMP** production after stimulation with isoproterenol and PGE1. The lymphocytic beta-adrenergic cascade exhibited homologous and heterologous desensitization 3 h after the use of epinephrine or thrombin, indicating that epinephrine administration was not a causative factor.

2000

10/3,AB/26 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13188334 BIOSIS NO.: 200100395483
Is the beneficial antidepressant effect of coadministration of pindolol really due to somatodendritic autoreceptor antagonism?
AUTHOR: Cremers Thomas I F H(a); Wiersma Loes J; Bosker Fokko J; den Boer Johan A; Westerink Ben H C; Wikstrom Hakan V
AUTHOR ADDRESS: (a)Department of Medicinal Chemistry, University of

Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen**Netherlands
JOURNAL: Biological Psychiatry 50 (1):p13-21 July 1, 2001
MEDIUM: print
ISSN: 0006-3223
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background: We investigated the combination of selective serotonin reuptake inhibitors (SSRIs) with the beta-adrenoceptor/serotonin 1A (5-HT1A) **antagonist** pindolol, based on the concept that 5-HT1A receptor blockade would eliminate the need for desensitization of presynaptic 5-HT1A receptors and therefore hasten the onset of action and improve the efficacy of SSRIs. However, since pindolol plasma levels after 2.5 mg three times a day are about 60 nmol/L, and the Ki for the 5-HT1A receptor is 30 nmol/L, it is questionable whether pindolol levels in the brain would be sufficient to antagonize 5-HT1A receptors. Using microdialysis in the guinea pig, we correlated brain and plasma levels of pindolol with its capability of augmenting paroxetine-induced increases in brain 5-HT levels. In addition, central beta-receptor antagonism of pindolol was studied by investigating blockade of beta-agonist-induced increases in brain cyclic adenosine monophosphate (**cAMP**) formation. Methods: Using microdialysis and jugular vein catheterization, we studied the ability of systemically **administered** pindolol to antagonize central 5-HT1A and beta-adrenoceptors, while simultaneously monitoring pindolol plasma and brain concentrations. Results: Augmentation of paroxetine-induced increases in extracellular 5-HT levels in the ventral hippocampus was only observed at steady state plasma levels exceeding 7000 nmol/L (concurrent brain levels 600 nmol/L). In contrast, antagonism of beta-agonist-induced increases of brain **cAMP** levels was already observed at pindolol plasma levels of 70 nmol/L (concurrent brain levels < 3 nmol/L) Conclusions: At plasma levels that are observed in patients after 2.5 mg three times a day (apprx60 nmol/L), pindolol produces only a partial blockade of presynaptic 5-HT1A autoreceptors and does not augment the SSRI-induced 5-HT increase in the guinea pig brain. It is therefore very unlikely that the favorable effects of combining pindolol with SSRIs, as reported in a number of clinical studies, are due to 5-HT1A antagonism. Since pindolol completely blocks central beta-adrenoreceptors at clinically relevant plasma levels, it is possible that beta-adrenoceptor antagonism is involved in mediating pindolol's beneficial effects.

2001

10/3,AB/27 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09727799 BIOSIS NO.: 199598182717
Activation of CFTR Cl- conductance in polarized T84 cells by luminal extracellular ATP.
AUTHOR: Stutts M Jackson(a); Lazarowski Eduardo R; Paradiso Anthony M; Boucher Richard C
AUTHOR ADDRESS: (a)CB 7020, Univ. North Carolina at Chapel Hill, Chapel Hill, NC 27599-7020**USA
JOURNAL: American Journal of Physiology 268 (2 PART 1):pC425-C433 1995
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Luminal extracellular ATP evoked a bumetanide-sensitive short-circuit current in cultured T84 cell epithelia (90.2 +- 18.2 mu-A/cm-2 at 100 mu-M ATP, apparent 50% effective concentration, 11.5 mu-M). ATP appeared to increase the Cl- conductance of the apical membrane but not the driving force for Cl- secretion determined by basolateral membrane K+ conductance. Specifically, the magnitude of Cl-secretion stimulated by ATP was independent of basal current, and forskolin pretreatment abolished subsequent stimulation of Cl- secretion by ATP. Whereas ATP stimulated modest production of adenosine 3',5'-cyclic monophosphate (**cAMP**) by T84 cells. ATP caused smaller increases in intracellular Ca-2+ and inositol phosphate activities than the Ca-2+-signaling Cl- secretagogue carbachol. An inhibitor of 5'-nucleotidase, alpha,beta-methyleneadenosine 5'-diphosphate, blocked most of the response to luminal ATP. The adenosine receptor **antagonist** 8-(p-sulfophenyl)theophylline blocked both the luminal ATP-dependent generation of **cAMP** and Cl- secretion when **administered** to the luminal but not submucosal bath. These results demonstrate that the Cl- secretion stimulated by luminal ATP is mediated by a A-2-adenosine receptor located on the apical cell membrane. Thus metabolism of extracellular ATP to adenosine regulates the activity of cystic fibrosis transmembrane conductor regulator (CFTR) in the apical membrane of polarized T84 cells.

1995

10/3,AB/28 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08294598 BIOSIS NO.: 000094065896
EFFECT OF H-2-BLOCKERS CIMETIDINE AND FAMOTIDINE ON HISTAMINE NASAL PROVOCATIVE TEST
AUTHOR: OGINO S; IRIFUNE M; HARADA T; MATSUNAGA T
AUTHOR ADDRESS: DEP. OTOLARYNGOL., OSAKA UNIVERSITY MED. SCH., 1-1-50, FUKUSHIMA, FUKUSHIMA-KU, OSAKA 553, JAPAN.
JOURNAL: ORL (OTO-RHINO-LARYNGOL) (BASEL) 54 (3). 1992. 152-154. 1992
FULL JOURNAL NAME: ORL (Oto-Rhino-Laryngology) (Basel)
CODEN: ORLJA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The H2-receptor is considered to mediate the stabilization of the membrane of mast cells by enhancing **cAMP** synthesis. In the present study, we investigated the effect of H2-receptor **antagonists**, i.e. H2-blockers, on nasal hypersensitivity using a histamine nasal provocative test. A 7-day administration of cimetidine tended to lower the histamine threshold. Famotidine **administered** in the same way caused no significant decrease in the histamine threshold. Based on the above results, we postulate that famotidine should be preferred to cimetidine as an H2-blocker in patients with gastric and/or duodenal ulcers.

1992

10/3,AB/29 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06678280 BIOSIS NO.: 000087120457
CHARACTERIZATION OF A MONOCLONAL ANTIBODY WHICH INHIBITS THE BIOLOGICAL ACTIVITY OF **HUMAN** CHORIONIC GONADOTROPIN IN **HUMAN** CORPORA LUTEA

AUTHOR: HAHLIN M; LINDBLOM B; SCHUURS A; KLOOSTERBOER H; HAMBERGER L
AUTHOR ADDRESS: DEP. OBSTETRICS AND GYNAECOLOGY, UNIV. GOTEBORG, SWEDEN.
JOURNAL: HUM REPROD (OXF) 4 (2). 1989. 152-157. 1989
FULL JOURNAL NAME: Human Reproduction (Oxford)
CODEN: HUREE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In the present study a murine monoclonal antibody (MCA), directed against **human** chorionic gonadotrophin (HCG), was investigated in vitro utilizing **human** corpora lutea (CL). The CL were excised from women of fertile age undergoing various gynaecological operations. The CL specimens were cut into pieces and incubated in standard medium for 2 or 4 h in the presence of HCG, luteinizing hormone (HLH) or prostaglandin (PG) E2 alone or in combination with the MCA directed against HCG. After incubation, the tissue levels of cyclic adenosine 3',5' monophosphate (**cAMP**) and the media contents of progesterone (P) were determined. HCG, HLH and PGE2 stimulated both **cAMP** and P formation in CL of all ages, while the MCA alone had no effect on these parameters. The MCA, however, effectively counteracted the stimulatory effect of HCG on both **cAMP** and P formation on a 1:1 molar basis. This **antagonistic** effect was clearly reversible and could be overcome by increasing the HCG concentrations. The stimulatory effect of HLH and PGE2, on the other hand, was not influenced by the antibody, even when **administered** at high concentrations. These in-vitro data show that the MCA studied effectively counteracts the stimulatory effect of HCG on **human** luteal tissue with high specificity.

1989

10/3,AB/30 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04767943 BIOSIS NO.: 000080071070
MARIHUANA-DERIVED MATERIAL BIOCHEMICAL STUDIES OF THE OCULAR RESPONSES
AUTHOR: GREEN K; CHEEKS K; MITTAG T; RILEY M V; SYMONDS C M; DEUTSCH H M; HODGES L C; ZALKOW L H
AUTHOR ADDRESS: DEP. OPHTHALMOL., MED. COLL. GA., MCG BOX 3059, AUGUSTA, GA. 30912, USA.
JOURNAL: CURR EYE RES 4 (5). 1985. 631-640. 1985
FULL JOURNAL NAME: Current Eye Research
CODEN: CEYRD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Some biochemical factors of the iris-ciliary body of the rabbit have been examined for effects induced by water-soluble marihuana-derived material (MDM). Adenylate cyclase activity and sensitivity to .beta.-adrenergic agonists were unchanged, as measured 4 h after MDM administration in vivo. Mg-dependent and anion-sensitive, but not Na-K, ATPase activities were inhibited 6 h after MDM administration in vivo, although they were unaffected by in vitro incubation. Topical administration of a potent substance P **antagonist** had no effect on the time course or magnitude of i.v. MDM-induced ocular effects in rabbit. I.v. **administered** sugars antagonized the effects of MDM on intraocular pressure. A variety of drugs which display a range of biochemical effects varying from .beta.-adrenergic receptor agonism, to alteration of glycoprotein residues were employed. None of the agents employed, ranging from **cAMP** modifiers to protein synthesis blockers, had any effect on the MDM-induced response. The mechanism underlying the ocular hypotensive effect of MDM may not reside in mediation through adenylate cyclase, ATPase or substance P, but rather

through a mechanism mediated by terminal sugar moieties on the molecule. Apparently, modification of the surface membrane glycoprotein residues on the ciliary epithelium can induce marked alterations in aqueous **human** flow rate.

1985

the percentage of apoptotic cells in response to 8-CPT-**cAMP** (1.3-fold, n = 6, P = 0.045) compared to B-precursor cells, and a smaller decrease in Mcl-1 levels (1.5-fold, n = 4, P = 0.014). Taken together, these findings show that **cAMP** is important in the regulation of apoptosis in B-progenitor and mature B cells and suggest that **cAMP** -increased apoptosis could be mediated, at least in part, by a decrease in Mcl-1 levels.

20/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10127120 99113788 PMID: 9916750
Increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency.
Aukrust P; Aandahl E M; Skalhegg B S; Nordoy I; Hansson V; Tasken K; Froland S S; Muller F
Research Institute for Internal Medicine, Medical Department A, Rikshospitalet, Oslo, Norway. pal.aukrust@klinmed.uio.no
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jan 15 1999, 162 (2) p1178-85, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The molecular mechanisms underlying the T cell dysfunction often present in common variable immunodeficiency (CVI) are not established. **cAMP** -dependent protein kinase A type I (PKAI) is an important inhibitor of T cell proliferation after Ag stimulation. We therefore investigated the possibility that activation of PKAI may be involved in the development of T cell dysfunction in CVI. An exogenously added PKAI-selective antagonist (**Rp**-8-**Br** -cAMPS) induced a significant increase in anti-CD3-stimulated PBMC proliferation in 20 CVI patients compared with no effect in 15 controls. Purified T cells from 7 CVI patients with strictly defined T cell deficiency had elevated endogenous **cAMP** levels compared with controls. **Treatment** of T cells from these CVI patients with **Rp**-8-bromo-**cAMP** -phosphorothioate markedly improved anti-CD3-stimulated proliferation (up to 3.7-fold), particularly in CD4+ lymphocytes, reaching proliferation levels comparable to control values. No effect of **cAMP** antagonist on T cell proliferation was seen in controls. In these CVI patients, **cAMP** antagonist also increased IL-2 production in anti-CD3-stimulated T cells. However, exogenously added IL-2 at concentrations comparable to the achieved increase in IL-2 levels after addition of **cAMP** antagonist had no effect on T cell proliferation. Furthermore, the stimulatory effects of exogenously added IL-2 at higher concentrations and **cAMP** antagonist on T cell proliferation were additive. Our findings indicate that increased PKAI activation may be an important molecular basis for the T cell defect in CVI and suggest that the **cAMP** /PKAI system may be a potential molecular target for immunomodulating therapy in these patients.

20/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09886841 98319630 PMID: 9657525
Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients.
Aandahl E M; Aukrust P; Skalhegg B S; Muller F; Froland S S; Hansson V; Tasken K
Institute of Medical Biochemistry, University of Oslo, Norway.
FASEB journal : official publication of the Federation of American Societies for Experimental Biology (UNITED STATES) Jul 1998, 12 (10) p855-62, ISSN 0892-6638 Journal Code: 8804484

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Cyclic AMP-dependent protein kinase A (PKA) type I has been established as an acute inhibitor of T cell activation. For this reason, we investigated the possible role of PKA type I in HIV-induced T cell dysfunction. T cells from HIV-infected patients have increased levels of **cAMP** and are more sensitive to inhibition by **cAMP analog** than are normal T cells. A PKA type I-selective antagonist increases the impaired proliferation of T cells from HIV-infected patients to normal or subnormal levels (up to 2.8-fold). Follow-up of patients after initiation of highly active antiretroviral **treatment** revealed that a majority of patients have a persistent T cell dysfunction that is normalized by incubation of T cells with **Rp**-8-**Br**-cAMPS. These observations imply that increased activation of PKA type I may contribute to the progressive T cell dysfunction in HIV infection and that PKA type I may be a potential target for immunomodulating therapy.

20/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09657364 98074740 PMID: 9413929

Altered cyclic AMP-dependent **human** chorionic gonadotropin production in cultured **human** placental trophoblasts exposed to ethanol.

Karl P I; Divald A; Diehl A M; Fisher S E
Department of Pediatrics, North Shore University Hospital-New York University School of Medicine, Manhasset, NY 11030, USA.

Biochemical pharmacology (ENGLAND) Jan 1 1998, 55 (1) p45-51, ISSN 0006-2952 Journal Code: 0101032
Contract/Grant No.: AA07284; AA; NIAAA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Chronic ethanol abuse during pregnancy can cause fetal injury, including the fetal alcohol syndrome (FAS). A contributing factor in this fetal injury may be the effect of ethanol on placental function. Previous studies have shown that ethanol **treatment** increases **human** chorionic gonadotropin (hCG) production by cultured **human** placental trophoblasts. In this study, we demonstrated that the stimulation of hCG production correlates with the ethanol concentration. Ethanol **treatment** enhanced intracellular adenosine 3':5'-cyclic monophosphate (**cAMP**) levels in response to either cholera toxin (CTX) or forskolin (FSK). Moreover, basal (i.e. unstimulated) **cAMP** levels were increased at 2 hr of ethanol exposure. However, this effect did not persist throughout the 24-hr incubation period. Therefore, ethanol **treatment** appears to induce increased hCG production, secondary to enhanced basal or stimulated **cAMP** production. The effect of ethanol was not associated with changes in Gs or Gi2 expression, as determined by northern blot and western blot analyses. In plasma membrane preparations from ethanol-**treated** cells, **cAMP** production was higher in response to Mn2+, a direct stimulator of adenylyl cyclase. Inclusion of **Rp-cAMP**, a protein kinase A inhibitor, eliminated the ethanol effect on hCG production. **Treatment** of cells with 8-**Br-cAMP** stimulated hCG production, but there was no difference between the ethanol-naive control and the ethanol-**treated** cells. These data suggest that ethanol **treatment** increases in vitro hCG production in **human** placental trophoblasts by enhancing **cAMP** production. Ethanol **treatment** appears to increase trophoblast adenylyl cyclase activity.

20/3,AB/6 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13739918 BIOSIS NO.: 200200368739
Inhibition of the leukocyte fluid shear response by glucocorticoid.
AUTHOR: Fukuda Shunichi(a); Yasu Takanori(a); Mitsuoka Hiroshi(a); Schmid-Schonbein Geert W(a)
AUTHOR ADDRESS: (a)Microcirculation Laboratory, Dept. of Bioengineering, Whitaker Institute for Biomedical Engineering, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0412**USA
JOURNAL: FASEB Journal 16 (4):pA518 March 20, 2002
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Physiological fluid shear controls pseudopod projection in leukocyte. It serves to maintain circulating leukocytes in a passive, overall spherical state as basic requirement for their normal circulation. We examine the hypothesis that glucocorticoids inhibit the leukocyte shear response by suppression of Ca2+ channel closure. Fresh **human** leukocytes adherent on a glass surface retract pseudopods during shear application with a slight decrease in intracellular Ca2+. In contrast, in dexamethasone-**treated** leukocytes, shear stress induces pseudopod projection with intracellular Ca2+ increase, which is inhibited by a voltage-dependent calcium channel blocker, diltiazem, or by **cAMP analog**, 8-**br**-**cAMP**. The A-kinase inhibitor, **Rp**-8-b-cAMPS, and high potassium ion concentrations induce pseudopod projection in response to fluid shear in a way similar to dexamethasone. The same reversed response could be observed in rat dexamethasone-**treated** leukocytes sheared with a cone and plate device. Thus glucocorticoids may reverse the fluid shear response of leukocytes by inhibition of the closure of voltage-dependent shear-sensitive Ca2+ channels by A-kinase.

2002

ds

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Set     Items   Description
S1     100172   CAMP
S2      32885   S1 AND HUMAN?
S3        454   S2 AND ADMINISTER?
S4          0   S3 AND PHARMACEUTICAL?
S5         63   S3 AND ANTAGONIST?
S6         51   RD (unique items)
S7          1   S6 AND IMMUNO?
S8         21   S6 AND TREAT?
S9          1   RP-8-BR-CAMPS
S10        30   S6 NOT S8
S11     12913   S1 AND ANALOG?
S12      3414   S11 AND TREAT?
S13      1222   S12 AND HUMAN?
S14      1222   S13 NOT S 5
S15        25   S14 AND ADMINISTER?
S16        20   RD (unique items)
? s s14 not s15
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              25  S15
     S17    1197  S14 NOT S15
? s s17 and br
            1197  S17
           23128  BR
     S18      73  S17 AND BR
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...examined 50 records  (50)
...completed examining records
     S19      55  RD (unique items)
? s s19 and rp
              55  S19
           19337  RP
     S20       6  S19 AND RP
? t s20/3,ab/all

 20/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10341011   99332312   PMID: 10402474
  IP-10 inhibits epidermal growth factor-induced motility by decreasing
epidermal growth factor receptor-mediated calpain activity.
  Shiraha H; Glading A; Gupta K; Wells A
  Department of Pathology, University of Alabama at Birmingham, Birmingham,
Alabama 35294-0007, USA.
  Journal of cell biology (UNITED STATES)   Jul 12 1999,  146  (1)  p243-54
,  ISSN 0021-9525   Journal Code: 0375356
  Contract/Grant No.: GM54739; GM; NIGMS
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  During wound healing, fibroblasts are recruited from the surrounding
tissue to accomplish repair. The requisite migration and proliferation of
the fibroblasts is promoted by growth factors including those that activate
the epidermal growth factor receptor (EGFR). Counterstimulatory factors in
wound fluid are postulated to limit this response; among these factors is
the ELR-negative CXC chemokine, interferon inducible protein-10 (IP-10). We
report here that IP-10 inhibited EGF- and heparin-binding EGF-like growth
factor-induced Hs68 human dermal fibroblast motility in a
dose-dependent manner (to 52% and 44%, respectively, at 50 ng/ml IP-10),
whereas IP-10 had no effect on either basal or EGFR-mediated mitogenesis
(96 +/- 15% at 50 ng/ml). These data demonstrate for the first time a
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counterstimulatory effect of IP-10 on a specific induced fibroblast response, EGFR-mediated motility.To define the molecular basis of this negative transmodulation of EGFR signaling, we found that IP-10 did not adversely impact receptor or immediate postreceptor signaling as determined by tyrosyl phosphorylation of EGFR and two major downstream effectors phospholipase C-gamma and erk mitogen-activated protein kinases. Morphological studies suggested which biophysical steps may be affected by demonstrating that IP-10 **treatment** resulted in an elongated cell morphology reminiscent of failure to detach the uropod; in support of this, IP-10 pretreatment inhibited EGF-induced cell detachment. These data suggested that calpain activity may be involved. The cell permeant agent, calpain inhibitor I, limited EGF-induced motility and de-adhesion similarly to IP-10. IP-10 also prevented EGF- induced calpain activation (reduced by 71 +/- 7%). That this inhibition of EGF-induced calpain activity was secondary to IP-10 initiating a **cAMP**-protein kinase A-calpain cascade is supported by the following evidence: (a) the cell permeant **analogue** 8-(4-chlorophenylthio)-**cAMP** (CPT-**cAMP**) prevented EGF-induced calpain activity and motility; (b) other ELR-negative CXC chemokines, monokine induced by IFN-gamma and platelet factor 4 that also generate **cAMP** , inhibited EGF-induced cell migration and calpain activation; and (c) the protein kinase A inhibitor **Rp**-8-**Br** -cAMPS abrogated IP-10 inhibition of cell migration, cell detachment, and calpain activation. Our findings provide a model by which IP-10 suppresses EGF-induced cell motility by inhibiting EGF-induced detachment of the trailing edges of motile cells.

20/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10279273 99288865 PMID: 10362019

Activation of the **cAMP** signaling pathway increases apoptosis in **human** B-precursor cells and is associated with downregulation of Mcl-1 expression.

Myklebust J H; Josefsen D; Blomhoff H K; Levy F O; Naderi S; Reed J C; Smeland E B

Department of Immunology, The Norwegian Radium Hospital, Oslo. junehm@ulrik.uio.no

Journal of cellular physiology (UNITED STATES) Jul 1999, 180 (1) p71-80, ISSN 0021-9541 Journal Code: 0050222

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

During B- and T-cell ontogeny, extensive apoptosis occurs at distinct stages of development. Agents that increase intracellular levels of **cAMP** induce apoptosis in thymocytes and mature B cells, prompting us to investigate the role of **cAMP** signaling in **human** CD10+ B-precursor cells. We show for the first time that forskolin (which increases intracellular levels of **cAMP**) increases apoptosis in the CD10- cells in a dose-dependent manner (19%-94% with 0-1,000 microM forskolin after 48 hours incubation, IC50 = 150 microM). High levels of apoptosis were also obtained by exposing the cells to the **cAMP** **analogue** 8-chlorophenylthio-**cAMP** (8-CPT-**cAMP**). Specific involvement of **cAMP**-dependent protein kinase (PKA) was demonstrated by the ability of a **cAMP** antagonist, **Rp** -isomer of 8-bromo-adenosine- 3', 5'- monophosphorothioate (**Rp**-8-**Br** -cAMPS), to reverse the apoptosis increasing effect of the complementary **cAMP** agonist, Sp-8-**Br**-cAMPS. Furthermore, we investigated the expression of Bcl-2 family proteins. We found that **treatment** of the cells with forskolin or 8-CPT-**cAMP** for 48 hours resulted in a fourfold decline in the expression of Mcl-1 (n = 6, P = 0.002) compared to control cells. The expression of Bcl-2, Bcl-xL, or Bax was largely unaffected. Mature peripheral blood B cells showed a smaller increase in

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Set     Items   Description
S1     100172   CAMP
S2      32885   S1 AND HUMAN?
S3        454   S2 AND ADMINISTER?
S4          0   S3 AND PHARMACEUTICAL?
S5         63   S3 AND ANTAGONIST?
S6         51   RD (unique items)
S7          1   S6 AND IMMUNO?
S8         21   S6 AND TREAT?
S9          1   RP-8-BR-CAMPS
S10        30   S6 NOT S8
? s s1 and analog?
          100172  S1
          580757  ANALOG?
     S11   12913  S1 AND ANALOG?
? s s11 and treat?
           12913  S11
         3263219  TREAT?
     S12    3414  S11 AND TREAT?
? s s12 and human?
            3414  S12
        13765360  HUMAN?
     S13    1222  S12 AND HUMAN?
? s s13 not s 5
            1222  S13
               0  S 5
     S14    1222  S13 NOT S 5
? s s14 and administer?
            1222  S14
          395036  ADMINISTER?
     S15      25  S14 AND ADMINISTER?
? rd
...completed examining records
     S16      20  RD (unique items)
? t s16/3/ab.all
>>>'AB.ALL' not recognized as item list
? t s16/3/ab/all
>>>'AB' not allowed as item list
? t s16/3,ab/all

 16/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12922455   21823964   PMID: 11834444
  An investigation of the effect of the prostaglandin EP2 receptor agonist,
butaprost, on the human isolated myometrium from pregnant and
non-pregnant women.
  Duckworth N; Marshall K; Clayton J K
  School of Pharmacy, University of Bradford, Bradford, West Yorkshire, BD7
1DP, UK.
  Journal of endocrinology (England)  Feb 2002,  172  (2)  p263-9,  ISSN
0022-0795   Journal Code: 0375363
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The aim of this study was to compare the effect of two known spasmogens,
oxytocin and the stable thromboxane receptor mimetic, U46619, on
human myometrium treated with the prostaglandin E receptor
(EP2) agonist, butaprost (selective for the EP2 receptor). Strips of
myometrium from pregnant and non-pregnant donors were set up in a
superfusion apparatus. Butaprost was administered as a bolus dose and
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via infusion. During the infusion of 10(-6) M butaprost, spasmogens were **administered** as bolus doses. Butaprost caused dose-related inhibition of myometrial activity when **administered** as a bolus dose (3-100 nmol) and concentration-dependent inhibition during infusion studies (10(-8)-10(-5)M). Butaprost (10(-6)M) attenuated the response to U46619 (0.1-10 nmol) in pregnant myometrium, but this difference was not statistically significant. Responses of pregnant myometrium to oxytocin (0.01-0.1 nmol) were significantly attenuated (P<0.05) in the presence of butaprost (10(-6)M). Butaprost physiologically antagonised the oxytocin response, possibly by increasing intracellular **cAMP** levels. This antagonism was much more marked than that seen with butaprost and U46619. It is unclear why these two types of antagonism differ and this effect is currently being investigated further using other prostanoid and non-prostanoid agents.

16/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11363932 21448434 PMID: 11564711

Insertion of an N-terminal 6-aminohexanoic acid after the 7 amino acid position of glucagon-like peptide-1 produces a long-acting hypoglycemic agent.

Doyle M E; Greig N H; Holloway H W; Betkey J A; Bernier M; Egan J M

Diabetes Section, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA.

Endocrinology (United States) Oct 2001, 142 (10) p4462-8, ISSN 0013-7227 Journal Code: 0375040

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The use of glucagon-like peptide-1 (GLP-1) as a routine **treatment** for type 2 diabetes mellitus is undermined by its short biological half-life. A cause of degradation is its cleavage at the N-terminal HAE sequence by the enzyme dipeptidyl peptidase IV (DPP IV). To protect from DPP IV, we have studied the biological activity of a GLP-1 **analog** in which 6-aminohexanoic acid (Aha) is inserted between histidine and alanine at positions 7 and 8. We have compared the biological activity of this new compound, GLP-1 Aha(8), with the previously described GLP-1 8-glycine (GLP-1 Gly(8)) **analog**. GLP-1 Aha(8) (10 nM) was equipotent with GLP-1 (10 nM) in stimulating insulin secretion in RIN 1046-38 cells. As with GLP-1 Gly(8), the binding affinity of GLP-1 Aha(8) for the GLP-1 receptor in intact Chinese hamster ovary (CHO) cells expressing the **human** GLP-1 receptor (CHO/GLP-1R cells) was reduced (IC(50): GLP-1, 3.7 +/- 0.2 nM; GLP-1 Gly(8), 41 +/- 9 nM; GLP-1 Aha(8), 22 +/- 7 nM). GLP-1 Aha(8) was also shown to stimulate intracellular **cAMP** production 4-fold above basal at concentrations as low as 0.5 nM. However, it exhibited a higher ED(50) when compared to GLP-1 and GLP-1 Gly(8) (ED(50): GLP-1, 0.036 +/- 0.002 nM, GLP-1 Gly(8), 0.13 +/- 0.02 nM, GLP-1 Aha(8), 0.58 +/- 0.03 nM). A series of D-amino acid-substituted GLP-1 compounds were also examined to assess the importance of putative peptidase-sensitive cleavage sites present in the GLP-1 molecule. They had poor binding affinity for the GLP-1 receptor, and none of these compounds stimulated the production of intracellular **cAMP** in CHO/GLP-1R cells or insulin secretion in RIN 1046-38 cells. GLP-1 Aha(8) (24 nmol/kg) **administered** sc to fasted Zucker (fa/fa) rats (mean blood glucose, 195 +/- 32 mg/dl) lowered blood glucose levels to a nadir of 109 +/- 3 mg/dl, and it remained significantly lower for 8 h. Matrix-assisted linear desorption ionization-time of flight mass spectrometry of GLP-1 Aha(8) incubated with DPP IV (37 C, 2 h) did not exhibit an N-terminal degradation product. Taken together, these results show that insertion of Aha after the 7 position in GLP-1 produces an effective, long-acting GLP-1 **analog**, which may be useful in the **treatment** of type 2 diabetes mellitus.

16/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11181683 21195388 PMID: 11298841
Changes in binding of iodomelatonin to membranes of Leydig cells and steroidogenesis after prolonged in vitro exposure to melatonin.
Valenti S; Fazzuoli L; Giordano G; Giusti M
Department of Endocrinology and Metabolism, University School of Medicine, Genoa, Italy. magius@unige.it
International journal of andrology (England) Apr 2001, 24 (2) p80-6, ISSN 0105-6263 Journal Code: 8000141
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The aim of the present study was to investigate the effects of prolonged exposure to melatonin (MLT) on the binding of iodomelatonin to membranes of rat Leydig cells and the subsequent modulation of testosterone and cyclic adenocine monophosphate (**cAMP**) secretion from these cells by MLT itself. Leydig cells were Percoll-purified from adult rats and cultured in vitro with MLT (1--100 nmol/L) for 16 h. Binding assays with 2(125I)iodomelatonin were then performed; moreover, testosterone and **cAMP** secretion during an acute challenge with lutenizing hormone (LH) (20 mIU/mL for 3 h) was assayed by RIA. As a result of prolonged MLT administration, a decrease in maximum binding density (Bmax) and equilibrium dissociation constant (Kd) of the binding of 2(125I)iodomelatonin to purified cell membranes was noted. Higher testosterone and **cAMP** secretion during LH challenge were recorded in cells pre-incubated with MLT; notwithstanding, the inhibitory effect of acutely **administered** MLT on LH-challenged secretions was not only retained but also reinforced, as the IC50 was 30% lower in cells pre-**treated** with the higher concentration of MLT (100 nM). Cycloheximide administration (10 microg/mL for 16 h) did not prevent hyper-sensitization to LH challenge or to acute MLT administration on LH challenge. Pertussis toxin (180 ng/mL for 16 h) prevented hyper-sensitization to LH, but not to acutely **administered** MLT. Forskolin (10 nmol/L) administration abolished either phenomena. In conclusion, prolonged exposure to MLT modulates the secretion of testosterone by cultured rat Leydig cells. Although MLT receptors were reduced, hyper-sensitization to LH challenge and to acutely **administered** MLT on LH challenge were observed with the higher concentration of MLT. Reduction in intracellular **cAMP** as a result of prolonged administration of MLT, could be the primary cause of both phenomena. On the one hand, reduced **cAMP** could start re-arrangement of the G-proteins and thus LH-dependent adenylate cyclase sensitization. On the other hand, reduced **cAMP** could render the Leydig cells more responsive to MLT itself through a mechanism which does not involve G-protein re-arrangement.

16/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11045670 21029395 PMID: 11191111
8-Cl-adenosine-induced inhibition of colorectal cancer growth in vitro and in vivo.
Carlson C C; Chinery R; Burnham L L; Dransfield D T
Department of General Surgery, Medical College of Georgia, Augusta, USA.
Neoplasia (New York, N.Y.) (United States) Sep-Oct 2000, 2 (5) p441-8, ISSN 1522-8002 Journal Code: 100886622
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed

The **cAMP analogue** 8-Cl-**cAMP** induces apoptosis and inhibits proliferation of a wide variety of malignancies in vitro and in vivo with relatively little toxicity. The antitumor effects of this compound are thought to involve its ability to modulate type I protein kinase A (PKAI). However, a nontoxic metabolite of 8-Cl-**cAMP**, 8-Cl-adenosine, with no known activity against PKAI, exerts growth inhibitory effects in breast, ovary, pancreas, and colorectal cancer cells in vitro and accumulates in xenografted tumors after 8-Cl-**cAMP treatment** in vivo. To characterize further the antitumor effects of 8-Cl-adenosine in colorectal cancer, we examined its effects on cell growth in vitro (cell number, 3H-thymidine incorporation, and soft agar colony formation) using the isogenically matched colorectal cancer cell lines HCT116, HCT116-E6 (p53-depleted), and 80S14 (p21WAF1/Cip1-null). 8-Cladenosine inhibited cell growth by 89%, 74%, and 79%, respectively in HCT116, HCT116-E6, and 80S14 cells after a 72-hour exposure. Growth inhibition coincided with DNA endoreduplication and subsequent apoptosis. Furthermore, nontoxic doses of 8-Cl-adenosine **administered** i.p. twice weekly for 4 weeks to athymic mice suppressed growth of HCT116-derived xenografts by 50%. These results show that 8-Cl-adenosine exerts antitumor activity against colorectal cancer independent of p53 and p21WAF1/Cip1.

16/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10262133 99237570 PMID: 10221213

Is there a difference in the function of granulosa-luteal cells in patients undergoing in-vitro fertilization either with gonadotrophin-releasing hormone agonist or gonadotrophin-releasing hormone antagonist?

Lin Y; Kahn J A; Hillensjo T
Ciconia Clinics, Frederiksberg, Copenhagen, Denmark.

Human reproduction (Oxford, England) (ENGLAND) Apr 1999, 14 (4) p885-8, ISSN 0268-1161 Journal Code: 8701199
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Gonadotrophin-releasing hormone (GnRH) regulates gonadotrophin release. It has been shown that GnRH may have a direct effect on the ovary, as the addition of GnRH to granulosa cell cultures inhibits the production of progesterone and oestradiol. Specific GnRH receptors have been found to be present in rat and **human** granulosa cells. Desensitization of the pituitary by GnRH agonist has become common in in-vitro fertilization (IVF) **treatment**, usually by a long protocol of 2-3 weeks. With the introduction of GnRH antagonists, which produce an immediate blockage of the GnRH receptors, a much shorter exposure is needed of 3-6 days. The aim of this study was to evaluate the effect of a GnRH agonist (buserelin) and a GnRH antagonist (cetrorelix) on the function of granulosa cells cultured in vitro from IVF patients. Women were **treated** by IVF randomized either to have buserelin nasal spray from the luteal phase in the previous cycle or cetrorelix from day 6 of the cycle. Both groups had ovarian stimulation with **human** menopausal gonadotrophin (HMG) 150 IU daily, i.e. HCG was **administered** when the follicles were larger than 17 mm, and aspirated 36 h later. Granulosa cells, separated and washed from large follicles containing ova, were pooled. After 48 h of pre-incubation, the granulosa cells were cultured for 4 days in medium with either added testosterone or **cAMP** with or without HCG, with change of medium after 2 days. The progesterone and oestradiol concentrations in the culture medium were measured by immunological assay, and cellular protein was measured by microprotein assay. The results showed that granulosa cells from women **treated** with GnRH antagonist (cetrorelix) responded

earlier to the in-vitro hormone stimulation in terms of progesterone accumulation than women **treated** with the GnRH agonist (buserelin). This may have been due to difference in time of exposure to the **analogue** . The results may indicate that the luteal function is less impaired in GnRH antagonist **treatment** than in GnRH agonist **treatment**.

16/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10138607 99103929 PMID: 9886979
A novel plant-derived inhibitor of **cAMP**-mediated fluid and chloride secretion.
Gabriel S E; Davenport S E; Steagall R J; Vimal V; Carlson T; Rozhon E J
Department of Pediatric Gastroenterology, University of North Carolina, Chapel Hill, North Carolina 27599, USA.
American journal of physiology (UNITED STATES) Jan 1999, 276 (1 Pt 1) pG58-63, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: P30-DK-34987; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have identified an agent (SP-303) that shows efficacy against in vivo cholera toxin-induced fluid secretion and in vitro **cAMP**-mediated Cl- secretion. Administration of cholera toxin to adult mice results in an increase in fluid accumulation (FA) in the small intestine (FA ratio = 0.63 vs. 1.86 in control vs. cholera toxin-**treated** animals, respectively). This elevation in FA induced by cholera toxin was significantly reduced (FA ratio = 0.70) in animals **treated** with a 100 mg/kg dose of SP-303 at the same time as the cholera **treatment**. Moreover, when SP-303 was **administered** 3 h after cholera toxin, a dose-dependent inhibition of FA levels was observed with a half-maximal inhibitory dose of 10 mg/kg. In Ussing chamber studies of Caco-2 or T84 monolayer preparations, SP-303 had a significant effect on both basal current and forskolin-stimulated Cl- current. SP-303 also induced an increase in resistance that paralleled the observed decrease in current. These data suggest that SP-303 has an inhibitory effect on **cAMP** -mediated Cl- and fluid secretion. Thus SP-303 may prove to be a useful broad-spectrum antidiarrheal agent.

16/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09915541 98357884 PMID: 9694511
Prostaglandin E2 inhibits apoptosis in **human** neutrophilic polymorphonuclear leukocytes: role of intracellular cyclic AMP levels.
Ottonello L; Gonella R; Dapino P; Sacchetti C; Dallegri F
First Medical Clinic, Department of Internal Medicine, University of Genoa Medical School, Italy.
Experimental hematology (UNITED STATES) Aug 1998, 26 (9) p895-902, ISSN 0301-472X Journal Code: 0402313
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human neutrophilic polymorphonuclear leukocytes (neutrophils) are terminally differentiated cells that die by undergoing apoptosis. At present, the intracellular pathways governing this process are only partially known. In particular, although the adenylate cyclase-dependent generation of cyclic AMP (**cAMP**) has been implicated in the triggering of apoptosis in lymphoid cells, the role of the intracellular **cAMP** pathway in neutrophil apoptosis remains controversial. In the present

study, we found that two **cAMP**-elevating agents, prostaglandin E2 (PGE2) and the phosphodiesterase type IV inhibitor RO 20-1724, inhibit neutrophil apoptosis without inducing cell necrosis. When **administered** in combination, PGE2 and RO 20-1724 displayed additive effects. Moreover, neutrophil apoptosis was inhibited by a membrane-permeable **analog** of **cAMP**, dibutyryl-**cAMP**, in a dose-dependent manner. Finally, **treatment** of neutrophils with the protein kinase A inhibitor H-89 prevented PGE2- and RO 20-1724-induced inhibition of cell apoptosis. In conclusion, taking into account that PGE2 and other **cAMP** -elevating agents are well known downregulators of neutrophil functions, our results suggest that conditions favoring a state of functional rest, such as intracellular **cAMP** elevation, prolong the life span of neutrophils by delaying apoptosis.

16/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09181742 97057723 PMID: 8902062
Buspirone, a serotonin receptor agonist, increases CD4 T-cell counts and modulates the immune system in HIV-seropositive subjects.
Hofmann B; Afzelius P; Iversen J; Kronborg G; Aabech P; Benfield T; Dybkjaer E; Nielsen J O
Department of Clinical Immunology, Copenhagen University Hospitals, Hvidovre, Denmark.
AIDS (London, England) (UNITED STATES) Oct 1996, 10 (12) p1339-47, ISSN 0269-9370 Journal Code: 8710219
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: We have previously shown that drugs that decrease intracellular **cAMP** levels increase/restore the proliferative and cytotoxic capacity of T cells from HIV-seropositive subjects in vitro. Buspirone, a serotonin receptor agonist, indirectly decreases intracellular **cAMP** levels in T cells and has the same increasing/restoring effect on T-cell proliferation in lymphocytes from HIV-seropositive subjects in vitro. DESIGN: Buspirone was given as a single high dose to six HIV-seropositive subjects, or as continuous medication with increasing dosage over 6 weeks to nine HIV-seropositive subjects, with CD4 T-cell counts of 150-300 x 10(6)/l. RESULTS: Significant increases in CD4 T cells, CD4 percentage and CD4/CD8 ratio were found 1 week after a single high dose of buspirone was **administered** . With continuous administration, a significant increase in CD4 T cells was observed after 1 and 4 weeks. Serum HIV RNA showed a significant decrease 1 h after a single dose of buspirone was **administered**. With continuous administration of buspirone, plasma HIV RNA first increased within the first 2 weeks of **treatment** and then decreased towards and below baseline concurrently with a significant decrease in CD8T cells. The proliferative T-cell response to poke weed mitogen and membrane expression of IL-2R increased significantly during continuous **treatment** with a significant decrease in expression of HLA-DR on CD8+ T cells. Development of "flu-like' symptoms, so severe that two patients withdrew from the study and two patients ceased medication before time, was a clinical indication of modulation of the immune system by buspirone. CONCLUSION: The study shows that buspirone modulates the immune system and leads to changes in the CD4 and CD8 T-cell numbers, functional capacity, cell maturation and viral load.

16/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07675509 93201469 PMID: 8453569
Prevention of **human** pancreatic cancer cell-induced hepatic

metastasis in nude mice by dipyridamole and its **analog** RA-233.
Tzanakakis G N; Agarwal K C; Vezeridis M P
Surgical Service Veterans Administration Medical Center, Providence, Rhode Island.
Cancer (UNITED STATES) Apr 15 1993, 71 (8) p2466-71, ISSN 0008-543X Journal Code: 0374236
Contract/Grant No.: CA 07340; CA; NCI; CA 13943; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND. Several studies have provided evidence suggesting that platelets play a key role in tumor metastasis. A number of antiplatelet agents have been used to prevent tumor metastasis in animal models and **humans** . Antiplatelet agents, dipyridamole (adenosine transport inhibitor), and RA-233 (inhibitor of **cAMP** PDE) were used to prevent tumor-cell-platelet interactions both in in vitro and in vivo systems; however, the data were not very conclusive. METHODS. Our studies used dipyridamole and RA-233 alone and in combination to investigate their effects on **human** pancreatic tumor cells (RWP-2)-induced platelet aggregation in **human** blood and on hepatic metastasis in nude mice. To examine effects of dipyridamole and RA-233 on liver metastasis, the tumor cells (RWP-2) were injected intrasplenically in nude mice grouped into control, dipyridamole (8 mg/kg), RA-233 (8 mg/kg), and dipyridamole plus RA-233 (8 mg/kg each). The agents were **administered** intraperitoneally 1 hour before and 24 hours after the tumor cell injection. RESULTS. When dipyridamole and RA-233 were used alone, only weak to moderate effects were seen on RWP-2 tumor cell-induced platelet aggregation. However, these agents, when combined, strongly inhibited the tumor cell-induced aggregation in **human** platelet-rich plasma. In tumor metastasis experiments, reductions of approximately 70% in hepatic nodules and 90% in surface area occupied by the tumor were seen with the combination **treatment** (dipyridamole plus RA-233) as compared with the control group of mice. CONCLUSIONS. This study suggests that the combination of dipyridamole and RA-233 provides an effective intervention for the antithrombotic approach to the **treatment** of cancer metastases.

16/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07377386 92312744 PMID: 1319687
Surfactant protein C: hormonal control of SP-C mRNA levels in vitro.
Veletza S V; Nichols K V; Gross I; Lu H; Dynia D W; Floros J
Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115.
American journal of physiology (UNITED STATES) Jun 1992, 262 (6 Pt 1) pL684-7, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: HL-19752; HL; NHLBI; HL-38288; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have studied hormonal regulation of the surfactant protein C (SP-C) in fetal 18-dah rat lung explants. SP-C mRNA was detected in Northern blots with a specific rat SP-C cDNA probe and quantified by densitometry. **Treatment** of the explants with dexamethasone resulted in a dose-dependent increase of the SP-C mRNA level. Transcriptional assays have shown that the regulation of SP-C mRNA by dexamethasone involves a transcriptional step. Administration of the **cAMP analogues**, 8-bromoadenosine 3',5'-cyclic monophosphate (8-BrcAMP) or dibutyryl adenosine 3',5'-cyclic monophosphate (DBcAMP), produced a dose-dependent increase of SP-C mRNA levels, with maximum stimulation observed at 200 microM. The thyroid hormone T3 had no effect on SP-C mRNA levels, whether

administered alone or in combination with dexamethasone. Variation in the effects of the above hormones on three surfactant protein mRNAs, SP-A, SP-B and SP-C, indicates that the hormonal regulation of the surfactant proteins is a complex process and that each gene is, in part, differentially regulated.

16/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07293584 92233992 PMID: 1809590
Effects of topical calcipotriol on calcium metabolism in psoriatic patients: comparison with oral calcitriol.
Gumowski-Sunek D; Rizzoli R; Saurat J H
Dermatology Clinic, University Hospital, Geneva, Switzerland.
Dermatologica (SWITZERLAND) 1991, 183 (4) p275-9, ISSN 0011-9075 Journal Code: 0211607
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **analogue** of calcitriol, calcipotriol (MC 903, Daivonex) has been proven effective in the **treatment** of psoriasis, when given topically. However, the possible influence of cutaneously absorbed MC 903 on calcium metabolism is still unclear. We evaluated various parameters of calcium metabolism in 17 psoriatic patients **treated** for 5.4 +/- 2.3 (mean +/- SD) weeks with MC 903, on 16 +/- 6% of the body surface. The dose **administered** (100 g of Daivonex corresponding to 5 mg of MC 903) decreased the PASI score by 40.9 +/- 20.0% (p less than 0.001). Among these patients, 12 were studied before and after MC 903 therapy. In none could be detected any change in protein-adjusted calcium, ionized Ca, plasma levels of creatinine, alkaline phosphatase, osteocalcin, intact parathyroid hormone (PTH), calcidiol and calcitriol, or in daily or fasting urinary excretion of Ca or **cAMP** . After an MC-903-free period, 9 patients received 1.5 micrograms/day of calcitriol orally for 7 days. Whereas this **treatment** did not control the skin relapse in most of the patients, it induced a significant increase in plasma levels of protein-adjusted Ca and calcitriol, and in 24-hour urinary Ca excretion, as well as a significant fall in PTH as compared with pretreatment values. These results indicate that 150 micrograms/day of MC 903, despite a possible 1% absorption, i.e. a systemic dose of 1.5 micrograms, did not produce any detectable alteration of Ca metabolism, whereas an equivalent dose of oral calcitriol was associated with significant changes. The threshold dose of topical calcipotriol that might induce alterations similar to 1.5 micrograms/day of oral calcitriol remains to be evaluated.

16/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07133849 92067993 PMID: 1958031
Regulation of **human** tumor antigen expression by biological response modifiers (BRMs).
Guadagni F; Roselli M; Schlom J; Greiner J W
Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD.
Annali dell'Istituto superiore di sanita (ITALY) 1991, 27 (1) p71-8, ISSN 0021-2571 Journal Code: 7502520
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ongoing development of monoclonal antibody technology may eventually lead to the selective targeting of **human** carcinoma lesions of MoAbs

conjugated with a variety of cytotoxic agents (i.e. radionuclides, drugs, etc.). The antigen phenotype of the carcinoma cell will play an important role in the efficacy of the MoAbs. Clearly, the **human** tumor antigens that are expressed on all carcinoma cells and with a high antigen density should provide the optimal target for the MoAbs. More often, however, the **human** tumor antigens whose expression is highly selective for **human** tumor cells will also exhibit a certain degree of heterogeneity. Therefore, the ability of a cytokine, such as interferon or 8-Cl-**cAMP**, to augment the level of expression of **human** tumor antigens such as TAG-72 and CEA, may play an important role in an adjuvant setting for immunoscintigraphy and/or immunotherapy. Further research will focus on experimental model system as well as clinical trials to determine whether **human** recombinant interferon **administered** with an anti-carcinoma MoAb will be an effective combination to enhance tumor detection and/or therapy. It is conceivable that in subsequent years effective approaches of **treating** malignancies may include a new combination of biological/immunological therapy based on the biology of the tumor cell population.

16/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06721585 91031237 PMID: 2171907
Receptor-mediated actions of growth hormone releasing factor on granulosa cell differentiation.
Moretti C; Bagnato A; Solan N; Frajese G; Catt K J
Endocrinology and Reproduction Research Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda MD 20892.
Endocrinology (UNITED STATES) Nov 1990, 127 (5) p2117-26, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
GRF promotes follicular maturation and ovulation when **administered** with FSH in the **treatment** of infertility. Such actions could be mediated by stimulation of GH secretion and insulin-like growth factor I production, but the known actions of the structurally related hormone, vasoactive intestinal peptide (VIP), on granulosa cell function suggested that GRF may also act directly on the ovary to stimulate follicular development. Radioligand binding and activation studies, performed in granulosa cells from immature estrogen-**treated** rats, revealed a common receptor for VIP and rat (r) GRF in the ovary. Specific binding of [125I]VIP to granulosa cells was saturable and dependent on time and temperature. The relative potencies of VIP-related peptides for inhibition of radioligand binding were: VIP greater than rGRF greater than peptide histidine isoleucinamide greater than [His1,Nle27] **human** GRF(1-32)NH2 greater than secretin. In binding studies with the potent GRF agonist, [125I] [His1,Nle27]GRF(1-32)NH2, relative potencies were: rGRF(1-43)OH greater than [His1,Nle27]**human** GRF(1-32)NH2 greater than VIP greater than peptide histidine isoleucinamide greater than secretin. Glucagon and gastric inhibitory peptide, other peptides of the glucagon superfamily, and unrelated peptides including CRF and beta-endorphin, did not inhibit binding of either radioligand to ovarian receptors. In cultured granulosa cells, rGRF and VIP stimulated **cAMP** formation, consistent with coupling of their receptors to the adenylate cyclase system, and potentiated FSH-induced **cAMP** production. Both peptides also amplified FSH-induced progesterone biosynthesis, aromatase activity, and LH receptor formation. These observations demonstrate that rGRF is a potent **cAMP** -mediated agonist in the rat ovary and acts on a common VIP/GRF receptor in maturing granulosa cells. It is likely that the potentiating effect of **administered** GRF on gonadotropin-stimulated follicular development in

vivo is in part mediated by direct actions of the peptide on the VIP/GRF receptor. Also, since GRF is present in the gonads, it is possible that the locally-produced peptide promotes follicular maturation by paracrine modulation of the stimulatory action of FSH on granulosa cell function.

16/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06311451 90005187 PMID: 2477231
Vasoactive intestinal polypeptide and alpha 2-adrenoceptor agonists regulate adenosine 3',5'-monophosphate accumulation and melatonin release in chick pineal cell cultures.
Pratt B L; Takahashi J S
Department of Neurobiology and Physiology, Northwestern University, Evanston, Illinois 60208.
Endocrinology (UNITED STATES) Nov 1989, 125 (5) p2375-84, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: F32-MH-09466; MH; NIMH; R37-MH-39592; MH; NIMH
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Vasoactive intestinal polypeptide (VIP) has been shown to stimulate melatonin synthesis in mammalian pineal; however, a regulatory role for VIP in the avian pineal has not been explored. Immunocytochemical and physiological response experiments were performed to investigate whether 1) immunoreactive VIP fibers innervated the avian pineal gland; 2) VIP had a specific effect on melatonin release that was mediated by **cAMP** stimulation; and 3) alpha 2-adrenergic signal transduction was associated with a reduction in **cAMP** levels. Immunocytochemical experiments demonstrated the presence of both tyrosine hydroxylase- and VIP-immunoreactive fibers in the avian pineal gland. **Treatment** of dispersed chick pineal cell cultures with VIP stimulated melatonin release (maximum 6-fold increase; EC50 = 1.8 nM) when **administered** during the 12-h light period of a 12-h light, 12-h dark cycle. Of the other four peptides tested [porcine VIP-(10-28), porcine peptide histidine isoleucine, porcine secretin, and **human** glucagon), only peptide histidine isoleucine stimulated melatonin release (EC50 = 30 nM). The effect of VIP was mediated by a time- and dose-dependent increase in **cAMP** accumulation (maximum 4-fold increase). The specific alpha 2-agonist UK-14,304 reduced **cAMP** accumulation (maximum 43% reduction) and inhibited melatonin release (EC50 = 19 nM) in the presence of 3 X 10(-8) M VIP. Norepinephrine-induced inhibition of nocturnal melatonin release was blocked by the elevation of **cAMP** achieved through the administration of forskolin (EC50 = 0.2 microM), isobutylmethylxanthine (EC50 = 112 microM), or 8-bromo-**cAMP** (EC50 = 166 microM). Collectively, these results demonstrate the presence and functional significance of VIP in the avian pineal gland, and the interaction of VIP and norepinephrine at the level of **cAMP** in the regulation of melatonin biosynthesis.

16/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05353254 87103865 PMID: 2433089
Carbocalcitonin **treatment** in Sudeck's atrophy.
Nuti R; Vattimo A; Martini G; Turchetti V; Righi G A
Clinical orthopaedics and related research (UNITED STATES) Feb 1987, (215) p217-22, ISSN 0009-921X Journal Code: 0075674
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The efficacy of new calcitonin, the amino **analog** of eel calcitonin (carboCT) on Sudeck's atrophy of the foot was investigated in 14 patients. CarboCT was **administered** at the dose of 40 Medical Research Council (MRC) units per day, and the duration of **treatment** was two to ten months. No adverse effects were noted. Bone pain and local edema decreased associated with improvement of motility. CarboCT induced a slight decrease in plasma calcium, plasma phosphate, and 24-hour urinary calcium excretion. An increase in **cAMP**/Cr ratio, an index of parathyroid function, was also observed (probably a manifestation of the hypocalcemic effect of calcitonin and secondary parathyroid stimulation). The whole body retention of 99mTc-MDP represents a valuable index of bone turnover, it decreased progressively and significantly on **treatment** . A dynamic study of local bone uptake of 99mTC-MDP was performed in eight patients. After carboCT therapy, statistically significant decreases in local blood flow, early uptake, and delayed uptake were appreciated in the involved foot. These findings lead to the conclusion that carboCT is effective in the **treatment** of Sudeck's atrophy.

16/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04584545 84271310 PMID: 6087215
Asu(1,7)E-CT, an **analog** of eel calcitonin. A comparative study in man with reference to other synthetic calcitonins]
La (Asu) E-CT, un **analogo** della calcitonina di anguilla. Studio comparativo nell'uomo rispetto ad altre calcitonine sintetiche.
Caniggia A; Nuti R; Vattimo A; Galli M; Turchetti V; Franci B; Martorelli T; Righi G
Minerva medica (ITALY) Apr 28 1983, 74 (18) p993-1010, ISSN 0026-4806 Journal Code: 0400732
Document type: Journal Article ; English Abstract
Languages: ITALIAN
Main Citation Owner: NLM
Record type: Completed
Asu) E-CT is a deaminodicarba-**analog** of the synthetic eel-calcitonin (E-CT) that shows specific activity and the potency reasonably high in comparison with that of the most potent natural hormone. The structure of its molecule indicates that the disulphide bond in calcitonins is not essential for the biological activity but only for the maintenance of the specific conformation by forming an intramolecular bridge. The instability of calcitonins should mainly be attributed to the presence of the disulfide bond and (Asu)E-CT proved to be more stable "in vitro" than native calcitonins. The more prolonged hypocalcemic effect of E-CT and its aminosuberic **analog** (Asu)E-CT has been accounted for to a greater stability of and persistence at the receptor site. (Asu) E-CT has been largely studied in Japan on experimental animals and successfully used in the **treatment** of hypercalcemia in man. On the contrary investigations on **human** administration of this **analog** are very scarce. The present paper reports studies carried out in normal subjects and Paget's disease patients to investigate the effects of (Asu)E-CT in man in comparison with the effects of synthetic **human** calcitonin (H-CT) and synthetic salmon calcitonin (S-CT). Two different experimental procedures have been used: 1) rapid intravenous injection of (Asu)E-CT (80 MRC. U.) or respectively of H-CT and S-CT (100 MRC. U.) in 15 subjects (7 normals and 8 with Paget's disease); 2) slow 7 days continuous subcutaneous infusion of similar daily amounts of (Asu)E-CT, H-CT and S-CT **administered** by a microjet pump device in 21 subjects (7 normals and 14 with Paget's disease). The intravenous administration of (Asu)E-CT induced a rapid and persistent decrease in total plasma calcium, ionized calcium and plasma phosphate that was more evident in Paget's disease patients than in normal subjects. No clearly cut differences have been observed with the hypocalcemic and hypophosphatemic effect of H-CT and S-CT **administered** intravenously; nevertheless the hypocalcemic effect

proved to be more persistent in Paget's disease patients **treated** with (Asu)E-CT. After intravenous infusion of (Asu)E-CT the plasma level of **cAMP** rose more evidently in pagetic than in normal subjects but the rise was lower than in H-CT and S-CT **treated** subjects.(ABSTRACT TRUNCATED AT 400 WORDS)

16/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04298883 83291405 PMID: 6309880
Probenecid inhibits the secretion of nephrogenous adenosine 3',5'-monophosphate in normal man.
Gogel E; Halloran B P; Strewler G J
Journal of clinical endocrinology and metabolism (UNITED STATES) Oct 1983, 57 (4) p689-93, ISSN 0021-972X Journal Code: 0375362
Contract/Grant No.: AM-07418; AM; NIADDK; AM-27319; AM; NIADDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Nephrogenous **cAMP**, that fraction of urinary **cAMP** secreted by the kidney, is PTH dependent and is used clinically as a measure of parathyroid function. To clarify the nature of secretion of nephrogenous **cAMP**, probenecid, an inhibitor of organic anion transport, was **administered** to eight healthy young males. Nephrogenous **cAMP** decreased after probenecid **treatment** (P less than 0.001), and plasma **cAMP** increased reciprocally (P less than 0.01) so that urinary **cAMP** did not change. There was no change in serum PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or urinary clearance of calcium or phosphate. These results suggest that secretion of nephrogenous **cAMP** may be a carrier-mediated process in normal man. The effect of probenecid to increase plasma **cAMP** is consistent with other observations suggesting that **cAMP** is cleared from plasma in part by a carrier-mediated process.

16/3,AB/18 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08845501 BIOSIS NO.: 199395134852
24,25-Dihydroxyvitamin D-3 **treatment** inhibits parathyroid-stimulated adenylate cyclase in iliac crest biopsies from uremic patients.
AUTHOR: Mortensen Berit M(a); Aarseth H P; Ganss R; Haug E; Gautvik K M; Gordeladze J O
AUTHOR ADDRESS: (a)Inst. Medical Biochem., Univ. Oslo, P.O. Box 1112, Blindern 0317 Oslo**Norway
JOURNAL: Bone (New York) 14 (2):p125-131 1993
ISSN: 8756-3282
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Renal osteodystrophy with increased bone resorption is a major clinical problem in patients with chronic renal failure. Previous reports have shown that threatment with 24,25-dihydroxy vitamin D-3 (24,25(OH)-2D-3) may result in decreased bone resorption. The present study addresses basic mechanisms for the action of 24,25(OH)-2D-3 in bone of patients with elevated serum parathyroid hormone (PTH) levels due to chronic renal disease. Twenty-four patients 56 +- 17 years old (mean +- SE) with chronic kidney disease in the predialytic state (serum creatinine gt 150 mu-mol/l) and elevated serum midregion PTH gt 1.2 mu-g/l were randomly assigned to oral **treatment** with either

1,25-dihydroxy vitamin D-3 (1,25(OH)-2D-3) (0.25-0.50 mu-g/day), 24,25(OH)-2D-3 (daily dose of 15 mu-g), or a combination of the two vitamin D-3 **analogs**. The control group received calcium carbonate (maximal dosage of 1 g times 3). Selected variables in serum and urine as well as hormone sensitive adenylate cyclase (AC) in iliac crest biopsies were assessed before **treatment** and during follow-up after two and six months. Serum levels of 1,25(OH)-2D-3 and 24,25(OH)-2D-3 were significantly (P lt 0.05) increased after two and six months in the respective **treatment** groups. Net bone PTH-enhanced AC (PTH-AC) fell abruptly (P lt 0.01) after two months of **treatment** and was nearly abolished (P lt 0.01) after six months with 24,25(OH)-2D-3 given alone or in combination with 1,25(OH)-2D-3. An inverse relationship (r = -0.57, P lt 0.05, n = 48) between net PTH-AC in bone and serum levels of 24,25(OH)-2D-3 was demonstrated. In all groups, serum total calcium (s-Ca) was maintained within normal range. Immunoreactive PTH was insignificantly altered by either of the vitamin D-3 **analogs** or by the combination regimen. These studies indicate that 24,25(OH)-2D-3 **administered** orally in pharmacological doses may represent an effective way to inhibit PTH-induced osseous **cAMP** production in uremic patients without causing significant side effects.

1993

16/3,AB/19 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03227726 BIOSIS NO.: 000071040837
TREATMENT OF THREATENED PREMATURE LABOR BY DRUGS
AUTHOR: CHIMURA T
AUTHOR ADDRESS: DEP. OBSTET. GYNECOL., YAMAGATA UNIV., SCH. MED., YAMAGATA.
JOURNAL: ACTA OBSTET GYNAECOL JPN (JPN ED) 32 (10). 1980. 1620-1624. 1980
FULL JOURNAL NAME: Acta Obstetrica et Gynaecologica Japonica (Japanese Edition)
CODEN: NISFA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Many reports describe the extent of uterine excitement in vitro and clinical conditions of uterine contractions at the time of threatened premature labor. Changes in blood levels of **cAMP**, Ca and prostaglandins appear to be the most useful parameters for uterine contraction and relaxation. The blood level of **cAMP** during threatened premature labor increased when any of the uterine inhibitors were **administered**. An inhibitory effect was seen with i.v. administration of dibutyryl **cAMP**, a **cAMP analog**. When the inhibitory effects against threatened premature labor by various inhibitors were classified by their inhibitory pattern, terbutaline and dibutyryl **cAMP** had the strongest and quickest effect; ethanol and indomethacin were weaker and slower in promoting the onset of their activities. Analysis of 263 cases of **treated** threatened premature labor demonstrated that there are 2 phases of contraction during premature labor: the active phase and the depressed phase. The active phase is best **treated** with .beta.2-stimulants; the drug of choice for the depressed phase can be varied to suit the clinical situation.

1980

16/3,AB/20 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02453415 BIOSIS NO.: 000066035959
1 DEAMINO-8-D ARGININE VASOPRESSIN **TREATMENT** OF CENTRAL DIABETES INSIPIDUS MECHANISM OF PROLONGED ANTI DIURESIS
AUTHOR: SEIF S M; ZENSER T V; CIAROCHI F F; DAVIS B B; ROBINSON A G
AUTHOR ADDRESS: DEP. MED., SCH. MED., UNIV. PITTSB., PITTSBURGH, PA. 15261, USA.
JOURNAL: J CLIN ENDOCRINOL METAB 46 (3). 1978 381-388. 1978
FULL JOURNAL NAME: Journal of Clinical Endocrinology & Metabolism
CODEN: JCEMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: DDAVP is a synthetic **analog** of arginine vasopressin which produces prolonged antidiuresis after intranasal administration to patients with complete central diabetes insipidus. The mechanism of the prolonged antidiuretic effect was studied by specific radioimmunoassay of DDAVP in plasma of patients and by in vitro studies on the adenylate cyclase-cyclic[c]AMP system of the rat outer renal medulla. When DDAVP was **administered** to patients, all responded, but the duration of response among patients varied from 5-21 h. The peak level of DDAVP in plasma was achieved up to 4 h after administration indicating a slow absorption from the nasal mucosa. The disappearance time of DDAVP from plasma correlated significantly with the duration of antidiuresis, $P < 0.001$. On a molar basis DDAVP was 3-fold greater than AVP in its stimulation of outer medullary adenylate cyclase activity and 10-fold greater than AVP in its stimulation of **cAMP** content. The prolonged antidiuresis of intranasally **administered** DDAVP is due to slow absorption, persistence in plasma and enhanced effect on the kidney.

1978

```
Set     Items   Description
S1       8018   CAMP
S2        528   S1 AND BR
S3         27   S2 AND (HIV OR AIDS OR CVI)
S4         26   RD (unique items)
S5        218   S2 AND (ANALOG? OR ANTAGONIST?)
S6        136   S5 AND (TREAT? OR ADMINISTER?)
S7        134   RD (unique items)
S8          7   S7 AND PKA
S9        127   S7 NOT S8
S10        96   S9 AND HUMAN?
S11        36   S10 AND RP
? s s10 not s11
              96  S10
              36  S11
     S12      60  S10 NOT S11
? s s12 and monobutyryl
              60  S12
              25  MONOBUTYRYL
     S13       0  S12 AND MONOBUTYRYL
? s s12 and chorophenyl
              60  S12
               2  CHOROPHENYL
     S14       0  S12 AND CHOROPHENYL
? s s12 and piperidino
              60  S12
             178  PIPERIDINO
     S15       0  S12 AND PIPERIDINO
```

ds

Set	Items	Description
S1	8018	CAMP
S2	528	S1 AND BR
S3	27	S2 AND (HIV OR AIDS OR CVI)
S4	26	RD (unique items)
S5	218	S2 AND (ANALOG? OR ANTAGONIST?)
S6	136	S5 AND (TREAT? OR ADMINISTER?)
S7	134	RD (unique items)
S8	7	S7 AND PKA

```
? s s7 not s8
             134  S7
               7  S8
      S9     127  S7 NOT S8
? s s9 and human?
             127  S9
         1002555  HUMAN?
     S10      96  S9 AND HUMAN?
? s s10 and rp
              96  S10
            8251  RP
     S11      36  S10 AND RP
? t s11/3,ab/all
>>>No matching display code(s) found in file(s): 304

 11/3,AB/1     (Item 1 from file: 156)
DIALOG(R)File 156:ToxFile
(c) format only 2002 The Dialog Corporation. All rts. reserv.

01295532   99113788   PMID: 9916750
  Increased activation of protein kinase A type I contributes to the T cell
deficiency in common variable immunodeficiency.
  Aukrust P; Aandahl E M; Skalhegg B S; Nordoy I; Hansson V; Tasken K;
Froland S S; Muller F
  Research Institute for Internal Medicine, Medical Department A,
Rikshospitalet, Oslo, Norway. pal.aukrust@klinmed.uio.no
  Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES)  Jan 15
1999, 162 (2) p1178-85, ISSN 0022-1767  Journal Code: 2985117R
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The molecular mechanisms underlying the T cell dysfunction often present
in common variable immunodeficiency (CVI) are not established. cAMP
-dependent protein kinase A type I (PKAI) is an important inhibitor of T
cell proliferation after Ag stimulation. We therefore investigated the
possibility that activation of PKAI may be involved in the development of T
cell dysfunction in CVI. An exogenously added PKAI-selective
antagonist (Rp-8-Br-cAMPS) induced a significant increase
in anti-CD3-stimulated PBMC proliferation in 20 CVI patients compared with
no effect in 15 controls. Purified T cells from 7 CVI patients with
strictly defined T cell deficiency had elevated endogenous cAMP
 levels compared with controls. Treatment of T cells from these CVI
patients with Rp-8-bromo-cAMP -phosphorothioate markedly
improved anti-CD3-stimulated proliferation (up to 3.7-fold), particularly
in CD4+ lymphocytes, reaching proliferation levels comparable to control
values. No effect of cAMP antagonist on T cell proliferation
was seen in controls. In these CVI patients, cAMP antagonist
also increased IL-2 production in anti-CD3-stimulated T cells. However,
exogenously added IL-2 at concentrations comparable to the achieved
increase in IL-2 levels after addition of cAMP antagonist had
no effect on T cell proliferation. Furthermore, the stimulatory effects of
exogenously added IL-2 at higher concentrations and cAMP
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antagonist on T cell proliferation were additive. Our findings indicate that increased PKAI activation may be an important molecular basis for the T cell defect in CVI and suggest that the **cAMP**/PKAI system may be a potential molecular target for immunomodulating therapy in these patients.

11/3,AB/2 (Item 2 from file: 156)
DIALOG(R)File 156:ToxFile

01229276 98074740 PMID: 9413929
Altered cyclic AMP-dependent **human** chorionic gonadotropin production in cultured **human** placental trophoblasts exposed to ethanol.
Karl P I; Divald A; Diehl A M; Fisher S E
Department of Pediatrics, North Shore University Hospital-New York University School of Medicine, Manhasset, NY 11030, USA.
Biochemical pharmacology (ENGLAND) Jan 1 1998, 55 (1) p45-51, ISSN 0006-2952 Journal Code: 0101032
Contract/Grant No.: AA07284; AA; NIAAA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chronic ethanol abuse during pregnancy can cause fetal injury, including the fetal alcohol syndrome (FAS). A contributing factor in this fetal injury may be the effect of ethanol on placental function. Previous studies have shown that ethanol **treatment** increases **human** chorionic gonadotropin (hCG) production by cultured **human** placental trophoblasts. In this study, we demonstrated that the stimulation of hCG production correlates with the ethanol concentration. Ethanol **treatment** enhanced intracellular adenosine 3':5'-cyclic monophosphate (**cAMP**) levels in response to either cholera toxin (CTX) or forskolin (FSK). Moreover, basal (i.e. unstimulated) **cAMP** levels were increased at 2 hr of ethanol exposure. However, this effect did not persist throughout the 24-hr incubation period. Therefore, ethanol **treatment** appears to induce increased hCG production, secondary to enhanced basal or stimulated **cAMP** production. The effect of ethanol was not associated with changes in Gs or Gi2 expression, as determined by northern blot and western blot analyses. In plasma membrane preparations from ethanol-**treated** cells, **cAMP** production was higher in response to Mn2+, a direct stimulator of adenylyl cyclase. Inclusion of **Rp-cAMP**, a protein kinase A inhibitor, eliminated the ethanol effect on hCG production. **Treatment** of cells with 8-**Br-cAMP** stimulated hCG production, but there was no difference between the ethanol-naive control and the ethanol-**treated** cells. These data suggest that ethanol **treatment** increases in vitro hCG production in **human** placental trophoblasts by enhancing **cAMP** production. Ethanol **treatment** appears to increase trophoblast adenylyl cyclase activity.

11/3,AB/3 (Item 1 from file: 442)
DIALOG(R)File 442:AMA Journals

00118645

The Genetics of Psoriasis 2001 The Odyssey Continues (ARTICLE)

ELDER, JAMES T.; NAIR, RAJAN P.; HENSELER, TILO; JENISCH, STEFAN; STUART, PHILIP; CHIA, NICHOLAS; CHRISTOPHERS, ENNO; VOORHEES, JOHN J.
Archives of Dermatology

NOV, 2001; Review: tzd1447
LINE COUNT: 00687

Accumulating evidence indicates that psoriasis is a multifactorial disorder caused by the concerted action of multiple disease genes in a single individual, triggered by environmental factors. Some of these genes control the severity of multiple diseases by regulating inflammation and immunity (severity genes), whereas others are unique to psoriasis. Various combinations of these genes can occur even within a single family, accounting in large measure for the many clinical manifestations of psoriasis. The disease-causing variants (alleles) of these genes probably arose early in the history of modern **humans**. As a result, psoriasis disease alleles are common in the general population, have a worldwide distribution, and often share the same ancestral chromosome with neutral alleles at adjacent loci. This phenomenon, called linkage disequilibrium, explains why psoriasis is strongly associated with HLA-Cw6 worldwide, although HLA-Cw6 is unlikely to be the disease allele. Many unaffected individuals carry 1 or more disease alleles, but lack other genetic and/or environmental factors necessary to produce disease. This explains why psoriasis develops in only about 10% of HLA-Cw6-positive individuals, and why genome-wide linkage scans for psoriasis and other multifactorial genetic disorders have not been uniformly successful. The **Human** Genome Project is rapidly generating a catalog of **human** DNA sequence variations. This resource has already allowed precise linkage disequilibrium mapping of the major histocompatibility complex psoriasis gene to just beyond HLA-C, toward HLA-A. This gene is likely to be identified soon. Further development and use of linkage disequilibrium resources will provide a powerful tool for the identification of the remaining psoriasis genes. Arch Dermatol. 2001;137:1447-1454

11/3,AB/4 (Item 2 from file: 442)
DIALOG(R)File 442:AMA Journals

00109024

Postexposure Prophylaxis After Nonoccupational HIV Exposure Clinical, Ethical, and Policy Considerations (ARTICLE)

LURIE, PETER; MILLER, SUELLEN; HECHT, FREDERICK; CHESNEY, MARGARET; LO, BERNARD
JAMA, The Journal of the American Medical Association
November 25, 1998; 20: tzj1769
LINE COUNT: 00615

In the wake of recent breakthroughs in antiviral therapies and Centers for Disease Control and Prevention (CDC) recommendations advocating occupational postexposure prophylaxis (PEP), health care workers are increasingly receiving inquiries about PEP following exposures to the **human** immunodeficiency virus (HIV) through sex and injection drug use. The probability of HIV transmission by certain sexual or injection drug exposures is of the same order of magnitude as percutaneous occupational exposures for which the CDC recommends PEP. In such cases, if the exposure is sporadic, it seems appropriate to extrapolate from the data on occupational PEP and recommend prophylaxis. However, for individuals with continuing or low-risk exposures, we instead recommend referrals to state-of-the-art risk reduction programs. Clinicians, using local HIV seroprevalence data and their knowledge of transmission probabilities, can help exposed patients make an informed decision regarding PEP. Because of the large number of risky encounters that will not be **treated** prophylactically, even after significant outreach efforts, public health interventions that emphasize PEP as part of a comprehensive HIV prevention

program should be confined to cities with highest HIV prevalences.JAMA. 1998;280:1769-1773

11/3,AB/5 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals

00107972

The Pathophysiological Significance of Nondesmoglein Targets of Pemphigus Autoimmunity Development of Antibodies Against Keratinocyte Cholinergic Receptors in Patients With Pemphigus Vulgaris and Pemphigus Foliaceus (ARTICLE)

NGUYEN, VU THUONG; LEE, TOU X.; NDOYE, ASSANE; SHULTZ, LEONARD D.; PITTELKOW, MARK R.; DAHL, MARK V.; LYNCH, PETER J.; GRANDO, SERGEI A.
Archives of Dermatology
Aug, 1998; Study: tzd971
LINE COUNT: 00864

Objectives: To determine whether nondesmoglein (non-Dsg) autoantibodies are pathogenic and whether they recognize keratinocyte cholinergic receptors that control cell adhesion because antikeratinocyte autoimmunity in patients with pemphigus vulgaris is not limited to the development of autoantibodies to Dsg. Design: To determine whether non-Dsg autoantibodies are pathogenic, we sought to induce pemphigus in genetically engineered neonatal mice lacking Dsg 3 using pemphigus vulgaris IgGs that did not cross-react with Dsg 1. To determine whether pemphigus autoimmunity involves keratinocyte cholinergic receptors, the latter were separated from cell membranes of **human** keratinocytes, tagged with the covalent label [/3/H]propylbenzilylcholine mustard, and used as an antigen in a radioimmunoprecipitation assay of 34 pemphigus vulgaris and 6 pemphigus foliaceus serum samples. Setting: The dermatologic clinics of the University of Minnesota, Minneapolis; the Mayo Clinic, Rochester, Minn; and the University of California-Davis Medical Center, Sacramento. Patients: Serum samples were collected from 34 patients with pemphigus vulgaris and 6 patients with pemphigus foliaceus (aged 31-89 years) and from 7 age-similar patients of both sexes with nonpemphigus blistering or the following immune-mediated conditions: pemphigoid gestationis, bullous drug eruption, lupus erythematosus, erythema nodosum, urticaria, acute contact dermatitis, and skin ulcers. Main Outcome Measures: Clinical, laboratory, and histopathologic findings. Results: Extensive skin blistering accompanied by the Nikolsky sign and suprabasilar acantholysis was induced in the Dsg3null/ mice that received pemphigus, but not normal **human** IgGs. In the radioimmunoprecipitation assays for reactivity with cholinergic receptors, the mean radioactivity precipitated by pemphigus serum samples significantly exceeded both normal- and disease-control levels (P,=,.001-.02). The mean individual levels of radioactivity precipitated by 34 pemphigus vulgaris and pemphigus foliaceus serum samples (85%) exceeded control values by a mean of approximately 2.6 times. Conclusions: Autoantibodies to keratinocyte cell-surface molecules other than Dsg 1 and Dsg 3 can induce clinical features of pemphigus vulgaris. Patients with pemphigus vulgaris and those with pemphigus foliaceus develop IgG antibodies that precipitate radiolabeled cholinergic receptors. Because these receptors control keratinocyte adhesion and motility, their inactivation by autoantibodies may elicit intracellular signals that cause disassembly of desmosomes, leading to acantholysis and blistering. Arch Dermatol. 1998;134:971-980

11/3,AB/6 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals

00104574

The Case for Sunscreens A Review of Their Use in Preventing Actinic Damage and Neoplasia (ARTICLE)

NAYLOR, MARK F.; FARMER, KEVIN C.
Archives of Dermatology
Sep, 1997; Review: tzd1146
LINE COUNT: 01713

Background: Recent controversy surrounding sunscreens has stimulated a reexamination of their use. The purposes of this article are to weigh the evidence regarding the value of sunscreens in preventing actinic damage and neoplasia and to evaluate the merit of objections that have been raised against their use for this purpose. Scientific aspects of damage from UV light, neoplasia, and sunscreens are reviewed. The value of sunscreen use in preventing actinic damage is discussed and a number of sunscreen controversies are revisited. Observations: The evidence favors the safety and efficacy of sunscreens for the prevention of actinic damage, melanoma, and nonmelanoma skin cancer. Conclusion: Sunscreens continue to be a practical and useful tool for the prevention of actinic damage and neoplasia. Arch Dermatol. 1997;133:1146-1154

11/3,AB/7 (Item 5 from file: 442)
DIALOG(R)File 442:AMA Journals

00095265

Signal Transduction Pathways Molecular Targets for Lithium's Actions (ARTICLE)

MANJI, HUSSEINI K.; POTTER, WILLIAM Z.; LENOX, ROBERT H.
Archives of General Psychiatry
July, 1995; News and Views: ps_531
LINE COUNT: 01209

Lithium remains the most widely used **treatment** for bipolar disorder, and this monovalent cation represents one of psychiatry's most important **treatments** . Despite its demonstrated efficacy in reducing both the frequency and severity of recurrent affective episodes and decades of clinical use, the molecular mechanisms underlying its therapeutic actions have not fully been elucidated. In this report, we review the exciting recent progress in the identification of key components of signal transduction pathways (in particular, guanine nucleotide-binding proteins [G proteins], adenylyl cyclases, and protein kinase C isozymes) as targets for lithium's actions and attempt to integrate these effects with the large body of data emphasizing alterations in various neurotransmitter (particularly monoaminergic) systems. Regulation of signal transduction within critical regions of the brain by lithium affects the function of multiple neurotransmitter systems and may thus explain lithium's efficacy in protecting susceptible individuals from spontaneous, stress-induced, and drug-induced cyclic affective episodes. Recent evidence has also demonstrated significant effects of lithium on the regulation of gene expression in the central nervous system, effects that may play a major role in the long-term stabilization of mood. The identification of these intracellular targets for lithium's actions offers the potential for the development of novel, improved therapeutic agents and, in conjunction with molecular genetic approaches, may facilitate our understanding of the

biological factors predisposing individuals to manic-depressive illness. (Arch Gen Psychiatry. 1995;52:531-543)

11/3,AB/8 (Item 6 from file: 442)
DIALOG(R)File 442:AMA Journals

00090922

Phospholipid Metabolite Expression by Head and Neck Squamous Cell Carcinoma (ARTICLE)

MANN, ERIC A.; SPIRO, JEFFREY D.; CHEN, LEI L.; KREUTZER, DONALD L.
Archives of Otolaryngology
July, 1994; Original Article: ot_763
LINE COUNT: 00479

Objective: To characterize the presence and production of various phospholipid metabolites by head and neck squamous cell carcinoma (HNSCC) and squamous cell carcinoma cell lines in vitro and in vivo. Design: The HNSCC tumor homogenates and supernatants of HNSCC tumorcultures and established squamous cell carcinoma cell lines were assayed for prostaglandin E2/ (PGE2/), leukotriene B4/ (LTB4/), and platelet activating factor (PAF). In vitro experiments were carried out under baseline conditions or with exposure to several known immunomodulators (epidermal growth factor, bacterial lipopolysaccharide, and interleukin 1). Patients: The HNSCC tumor tissue was obtained from primary tumor orcervical lymph node metastasis of surgical resections. Main Outcome Measures: Prostaglandin E2/, LTB4/, and PAF were measured in tumor homogenates and cell culture supernatants using standardized radioimmunoassay kits. Results: All tumor homogenates (eight of eight) contained detectable levels of PGE2/ (range, 324 to 2258 pg/g of tumor tissue) and LTB4/ (range, 790 to 41,900 pg/g of tumor tissue); PAF was detected in six of eight homogenates (range, 7362 to 40,788 pg/g of tumor tissue). All of the short-term primary HNSCC tumor cultures andsquamous carcinoma lines produced PGE2/ (range, 90 to 1160 pg/10/6/ cells), and half of the cultures produced LTB4/ (range, 100 to 1700 pg/10/6/ cells); none of the cultures or cell lines produced detectable levels of PAF. Interleukin 1 significantly enhanced production of PGE2/ by tumor cultures (P<.02). Characterization of tumor cultures with a fibroblast antibody marker, BR2, revealed that 26% to 64% of tumor culture cells were fibroblasts. Conclusions: Prostaglandin E2/, LTB4/, and PAF are present in the tumor microenvironment, where they may be involved in the local immunosuppression phenomenon seen in HNSCC. Both PGE2/ and LTB4/ wereproduced in vitro by tumor cultures and squamous cell carcinoma cell lines; PAF was not produced by tumor cultures in vitro and therefore may be a product of local immune cells in HNSCC in vivo. Interleukin 1 and PGE2/ may interact in immunoregulation in the HNSCC tumor microenvironment.
(Arch Otolaryngol Head Neck Surg. 1994;120:763-769)

11/3,AB/9 (Item 7 from file: 442)
DIALOG(R)File 442:AMA Journals

00090489

Serotonin and **Human** Myoclonus Rationale for the Use of Serotonin Receptor Agonists and **Antagonists** (ARTICLE)

Archives of Neurology
June, 1994; Neurological Review: ne_605

LINE COUNT: 01423

This is a critical review of the serotonin hypothesis of myoclonus for the purpose of identifying new pharmacologic therapies. The literature on myoclonus and serotonin neuropharmacology reveals evidence for serotonergic abnormalities in some **human** myoclonic disorders, new serotonin receptor subtypes and data on their molecular structure and function, more selective drugs, and experimental evidence linking certain serotonin receptor subtypes with myoclonus. This article provides an overview of clinical experience with serotonergic drugs, new investigational drugs, and strategies for gathering data critical to linking particular receptorabnormalities and drugs with specific **human** myoclonic disorders. Suchinformation will allow the use of receptor subtype-selective agonistsand **antagonists** for the **treatment** of myoclonus. (Arch Neurol. 1994;51:605-617)

11/3,AB/10 (Item 8 from file: 442)
DIALOG(R)File 442:AMA Journals

00086452

Psychobiologic Mechanisms of Posttraumatic Stress Disorder (ARTICLE)

CHARNEY, DENNIS S.; DEUTCH, ARIEL Y.; KRYSTAL, JOHN H.; SOUTHWICK, STEVEN M.; DAVIS, MICHAEL
Archives of General Psychiatry
April, 1993; News and Views: p294
LINE COUNT: 01540

11/3,AB/11 (Item 9 from file: 442)
DIALOG(R)File 442:AMA Journals

00086139

Coffee Facts and Controversies (ARTICLE)

ETHERTON, GALE M.
Archives of Family Medicine
Mar, 1993; CLINICAL REVIEW: p317
LINE COUNT: 00552

In this article, we review current literature on coffee, both regularand decaffeinated, and its potential effects in **humans**. Moderate coffee consumption is believed to have no persistent effect on blood pressure. Large intake of coffee may increase total cholesterol levels; boiled coffee increases cholesterol levels more than filteredcoffee. Consuming more than four cups per day may be associated with increased risk of acute myocardial infarction. There appears to be anassociation between urinary bladder cancer and coffee consumption. Noassociation was found between ingestion of coffee and incidence of duodenal ulcer and ulcerative colitis. Increased coffee consumption by pregnant women appears to decrease fetal birth weight. Fetal heartrate, respiration, and both maternal and fetal anemia are increased with coffee consumption but coffee has not been shown to be teratogenic. Coffee consumption appears to pose no particular threat in most people if consumed in moderation. Naturally decaffeinated, filter-brewed coffee further diminishes its potential harmful effects.

11/3,AB/12 (Item 10 from file: 442)
DIALOG(R)File 442:AMA Journals

00085647

The Hypothalamic-Pituitary-Adrenal-Immune Axis A Critical Assessment (ARTICLE)

LILLY, MICHAEL P.
Archives of Surgery
December, 1992; Basic: p1463
LINE COUNT: 01408

The hypothalamic-pituitary-adrenal (HPA) system has been a model for neuroendocrine control of responses of organisms to stressors since the turn of the century. Despite this, the pathways by which infectious insults interact with the HPA system remained poorly defined. Recently, evidence has been presented suggesting that humoral mediators released by inflammatory cells (cytokines) may parti- cipate in two-way communication between the site of inflammation and the central nervous system. In this review, we detail the current understanding of the responses of the HPA system to the classic physiologic stimuli of hypo- volemia and pain, with anemphasis on the cellular mechanisms and mediators discovered in recent years. We also examine the data substantiating a role of interleukin 1, interleukin 6, and tumor necrosis factor in the directhumoral activation of the HPA system and consider the evidence favoring a physiologic negative feedback relationship between the HPAand the immune systems. Such an interaction is an exciting concept with broad clinical implications. However, we believe that the temporal and quantitative aspects of experiments designed to evaluatethis interaction must be carefully evaluated to assure that true physiologic stimuli are studied and that the responses observed are not due to pharmacologic effects of inflammatory mediators acting through `classic' neuroendocrine pathways. (Arch Surg. 1992;127:)

11/3,AB/13 (Item 11 from file: 442)
DIALOG(R)File 442:AMA Journals

00055099

The Effects of Carbocisplatin and Radiation on Skin Flap Survival (Article)

Kleiman, Lee A., MD; Hasslinger, Brian, MD; Eddy, Hugh, PhD; Suter, Charles, PhD; Blanchard, Cyrus, MD; Gray, William, MD
Archives of Otolaryngology-Head & Neck Surgery
1992; 118: 68 (6)

Carbocisplatin is used as an inductive chemotherapeutic agent prior to irradiation in the **treatment** of head and neck cancers. Controversy exists whether carbocisplatin sensitizes normal epithelial tissues, including skin, to radiation. The combined effect of radiation and carbocisplatin on the survival of skin flaps was studied in an experimental model using dorsal flaps in Sprague-Dawley rats. Skin flaps were created 6 weeks after exposure to irradiation and carbocisplatin. Flap survival was assessed 7, 14, and 21 days after the flaps were initially created. Exposure of the flaps to irradiation alone, carbocisplatin alone, combined irradiation and carbocisplatin, or combined irradiation and fractionated carbocisplatin did not result in any significant decrease in flap survival when compared with untreated animals.

11/3,AB/14 (Item 12 from file: 442)
DIALOG(R)File 442:AMA Journals

00052388

Abnormalities of Cutaneous Blood Flow Regulation in Patients With Reflex Sympathetic Dystrophy as Measured by Laser Doppler Fluxmetry (Article)

Bej, Mark D., MD, Schwartzman, Robert J., MD
Archives of Neurology
1991; 48: 912 (4)

The response of cutaneous blood flow to autonomic stimuli was evaluated in eight patients with clinically staged reflex sympathetic dystrophy and eight healthy control subjects. Blood flow was measured in the affected and contralateral extremities by laser Doppler fluxmetry. Five autonomic stimuli were applied to the contralateral extremity during blood flow measurement in the ipsilateral affected extremity. Affected limbs of patients with reflex sympathetic dystrophy were found to have statistically significantly increased blood flow during the Valsalva maneuver and cold pressor test, while blood flow decreased in normal controls. No significant differences were found in limb temperature or baseline blood flow between patients and controls. Reflex sympathetic dystrophy stage did not affect response to the procedures. Control subjects demonstrated a rhythmic cycling of cutaneous blood flow that was absent in patients with reflex sympathetic dystrophy. These results support a central abnormality of the sympathetic nervous system in reflex sympathetic dystrophy.

11/3,AB/15 (Item 13 from file: 442)
DIALOG(R)File 442:AMA Journals

00051917

Cognitive Neuropsychology: Resolving Enigmas About Wernicke's Aphasia and Other Higher Cortical Disorders (Article)

Margolin, David Ira, MD, PhD
Archives of Neurology
1991; 48: 751 (15)

Cognitive neuropsychology is a young branch of neuroscience whose ancestral influences include a rich pool of experimental (eg, cognitive psychology), theoretical (eg, epistemology), and clinical (eg, neurology, neuropsychology) disciplines. An essential principle of cognitive neuropsychology is that disorders of higher cortical functions can be understood in terms of breakdowns of one or more information-processing modules. Each module is the most basic element of intelligence that can be defined based on current knowledge. This approach is a refinement of--not a fundamental departure from--the 19th-century "localizationist" view of language disorders. Wernicke's aphasia, for example, classically attributed to a single cognitive deficit (loss of word sounds), is shown in this review to require damage to multiple distinct information-processing modules. Cognitive neuropsychology provides the tools for the type of fine-grained analyses of behavior that are needed to capitalize on recent advances in neuroimaging techniques, including the development of more sophisticated models of brain-behavior relationships.

11/3,AB/16 (Item 14 from file: 442)
DIALOG(R)File 442:AMA Journals

00045043

Calcium Channel Blockers in Myocardial Infarction (CLINICAL OBSERVATIONS)

SKOLNICK, ALAN E.
Archives of Internal Medicine
July, 1989; 149: 1669-16771989;
LINE COUNT: 00676 WORD COUNT: 09332

ABSTRACT: Calcium channel blockers are currently approved for use in patients with arrhythmias, stable and unstable angina pectoris, and systemic hypertension. The hemodynamic and electrophysiologic properties of these agents suggest that their use would be appropriate in both the immediate and the long-term management of patients who suffered a myocardial infarction. Some experimental evidence accumulated from animal models supports the ability of these drugs to reduce both myocardial infarct size and the incidence of ventricular arrhythmias. The clinical trials with these drugs, however, have yielded disappointing results. Some data suggest a role of diltiazem therapy in reducing the incidence of transmural wall infarction and angina in those patients sustaining non-Q-wave myocardial infarctions. In the setting of Q-wave infarction, calcium channel blockers seem to be less effective than beta-blockade both for acute and long-term management. Finally, calcium channel blockers appear to be contraindicated in patients who have suffered a myocardial infarction and who have concomitant left ventricular dysfunction.

11/3,AB/17 (Item 15 from file: 442)
DIALOG(R)File 442:AMA Journals

00043825

Somatostatin and a Long-Acting **Analogue**, Octreotide Acetate; Relevance to Dermatology (>ER>)

CAMISA, CHARLES
Archives of Dermatology
March, 1989; 125: 407-4121989;
LINE COUNT: 00282 WORD COUNT: 03901

11/3,AB/18 (Item 16 from file: 442)
DIALOG(R)File 442:AMA Journals

00041135

Lymphocyte beta-Adrenergic Receptor Modification in Bulimia (ORIGINAL ARTICLE)

BUCKHOLTZ, NEIL S.; GEORGE, DAVID T.; DAVIES, ALBERT O.; JIMERSON, DAVID C.; POTTER, WILLIAM Z.
Archives of General Psychiatry
May, 1988; 45: 479-4821988;
LINE COUNT: 00220 WORD COUNT: 03038

ABSTRACT: beta-Adrenergic receptor binding on circulating lymphocytes was evaluated in young female bulimic patients (n = 12) and age- and

sex-matched normal control volunteers (n = 10). Using iodine 125-labeled cyanopindolol, **antagonist** binding was evaluated (number of receptors (B)max and dissociation constant (K)D), and using isoproterenol competition of cyanopindolol binding, the concentration required to inhibit binding by 50% (IC50) for isoproterenol and the agonist affinity measure of K(L)/K(H) (ratio of dissociation constants for the low- and high-affinity states of the receptor) were determined. Plasma norepinephrine (NE) level was also measured. There was a trend toward lower plasma NE levels in the bulimic patients. The K (L)/K(H) ratio in bulimic patients was significantly greater than that for the normal volunteers, indicating increased receptor coupling. The K(L)/K(H) ratio was not significantly correlated with plasma NE level. Neither B(max) nor K(D) was different between the two groups. These findings suggest that beta-adrenergic receptors in bulimic patients may be more responsive than in normal subjects, without alteration of the traditional measures of receptor responses, a difference that cannot be explained on the basis of plasma NE. These findings provide another line of evidence for altered regulation of the noradrenergic system in bulimic patients during a controlled phase of their illness.

11/3,AB/19 (Item 17 from file: 442)
DIALOG(R)File 442:AMA Journals

00034521

Long-term Effects of Topically Applied Epinephrine on the Blood-Ocular Barrier in **Humans** (CLINICAL SCIENCES)

MIYAKE, KENSAKU; MIYAKE, YOSHIKO; KURATOMI, RYOKO
Archives of Ophthalmology
October, 1987; 105: 1360-13631987;
LINE COUNT: 00195 WORD COUNT: 02702

ABSTRACT: Epinephrine (1.25%) was applied topically twice daily to both eyes of 22 patients with glaucoma or ocular hypertension. Half of these patients received topical indomethacin (0.5%) three times daily in one eye; the other half received indomethacin placebo under the same regimen. Blood-aqueous and blood-retinal barrier functions were determined by aqueous and vitreous fluorophotometry before and 1, 2, 3, and 7 months after initiation of **treatment**. Epinephrine-induced disruption of the blood-aqueous barrier, noted at two months, apparently remained constant until the completion of the study. At months 2, 3, and 7, indomethacin significantly inhibited this disruption. The blood-retinal barrier was unaffected. These results bear on the hypotensive mechanism of topically applied epinephrine.

11/3,AB/20 (Item 18 from file: 442)
DIALOG(R)File 442:AMA Journals

00032828

Intraocular Injection of Prostaglandins; Modification of Response to Circulating Bacterial Endotoxin (LABORATORY SCIENCES)

WONG, KEYE L.
Archives of Ophthalmology
February, 1983; 101: 275-2791983;
LINE COUNT: 00327 WORD COUNT: 04517

ABSTRACT: Circulating bacterial endotoxin in the rabbit produces a transient iridocyclitis. Alteration in the ocular vascular permeability was measured by accumulation of iodonated I 125 serum albumin. The role of local mediator release in modifying the effect of endotoxin was investigated by pretreatment with intravitreal injections of prostaglandin E 1 (alprostadil), prostaglandin E2 (dinoprostone), prostaglandin F(2a) (dinoprost), histamine dihydrochloride, histamine phosphate, bradykinin triacetate, and serotonin creatinine sulfate. Histamine, bradykinin, and serotonin by themselves did not produce an alteration in ocular vascular permeability in the manner studied, nor did their prior injection alter the ocular response to circulating endotoxin. By contrast, prostaglandin E1, prostaglandin E 2, and prostaglandin F(2a) produced an alteration in ocular vascular permeability. After resolution of this alteration, the eye became partially refractory to endotoxin-induced inflammation. Neither the production of an inhibitory substance nor cyclic adenosine monophosphate seemed to be involved in this decreased responsiveness. Possible mechanisms of this anti-inflammatory effect are discussed. (Arch Ophthalmol 1983;101:275-279)

11/3,AB/21 (Item 19 from file: 442)
DIALOG(R)File 442:AMA Journals

00028845

Prophylaxis Against Repeated Radiocontrast Media Reactions in 857 Cases; Adverse Experience With Cimetidine and Safety of beta-Adrenergic **Antagonists** (ORIGINAL INVESTIGATIONS)

GREENBERGER, PAUL A.; PATTERSON, ROY; TAPIO, CHARLENE M.
Archives of Internal Medicine
December, 1985; 145: 2197-22001985;
LINE COUNT: 00229 WORD COUNT: 03165

ABSTRACT: Eight hundred fifty-seven radiocontrast media (RCM) procedures were performed from 1974 to 1984 in 743 patients who previously had experienced an immediate generalized (anaphylactoid) reaction to RCM. During the 695 intravascular infusions of RCM, prednisone-diphenhydramine hydrochloride pretreatment of 415 essential repeated RCM procedures from 1974 to 1980 resulted in 45 (10.8%) reactions during which transient hypotension occurred in three (0.7%) patients. From 1980 to 1983, prednisone-diphenhydramine-ephedrine sulfate pretreatment of 180 procedures was associated with only nine reactions (5.0%) (chi-square=5.195). The addition of cimetidine hydrochloride in 1983 to 1984 was not useful in that 14 reactions occurred during 100 procedures (14.0%). The 21 patients who had been receiving beta-adrenergic **antagonist** therapy were protected as well as those who were not, in that none of 11 patients receiving the three-drug regimen had a repeated reaction and only one of ten patients receiving the four-drug regimen reacted.

11/3,AB/22 (Item 20 from file: 442)
DIALOG(R)File 442:AMA Journals

00026152

alpha-Adrenergic Receptor Function in Schizophrenia; Receptor Number, Cyclic Adenosine Monophosphate Production, Adenylate Cyclase Activity, and Effect of Drugs (ORIGINAL ARTICLES)

KAFKA, MARIAN S.
Archives of General Psychiatry
March, 1983; 40: 264-2701983;
LINE COUNT: 00310 WORD COUNT: 04278

ABSTRACT: alpha-Adrenergic receptor function was assessed in platelets from drug-free schizophrenic patients and control subjects. The number of alpha-receptors was similar in platelet membranes from schizophrenic patients and control subjects. In intact platelets from schizophrenic male, but not female, patients, prostaglandin E1 (PGE1)-stimulated cyclic adenosine monophosphate (**cAMP**) level was less than in control subjects. This defect may be due, at least in part, to decreased adenylate cyclase activity. In platelet lysates from schizophrenic patients, but not from normal control subjects, adenylate cyclase activity was diminished and PGE1-stimulated adenylate cyclase activity could be restored partially by the addition of guanosine triphosphate. **Treatment** with neuroleptic drugs or lithium carbonate did not change alpha-receptor number or **cAMP** production in platelets from schizophrenic patients, but high doses of propranolol hydrochloride increased **cAMP** production without affecting the number of alpha-receptors. If the production of **cAMP** in neurons is similar to that in platelets, diminished **cAMP** production may be associated with a vulnerability to schizophrenia. (Arch Gen Psychiatry 1983;40:264-270)

11/3,AB/23 (Item 21 from file: 442)
DIALOG(R)File 442:AMA Journals

00019205

The High-Affinity Receptor for Immunoglobulin E; Prospects for the Therapy of Immediate Hypersensitivity Reactions (SPECIAL COMMUNICATIONS)

DRESKIN, STEPHEN C.
JAMA, The Journal of the American Medical Association
September 2, 1988; 260: 1265-12681988;
LINE COUNT: 00221 WORD COUNT: 03058

11/3,AB/24 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00120380

Drug Therapy: Erectile Dysfunction (Review Articles)

Lue, Tom F.
The New England Journal of Medicine
Jun 15, 2000; 342 (24),pp 1802-1813
LINE COUNT: 00560 WORD COUNT: 07734

11/3,AB/25 (Item 2 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00120246

Medical Progress: The Acute Respiratory Distress Syndrome (Review Articles)

Ware, Lorraine B.; Matthay, Michael A.
The New England Journal of Medicine
May 4, 2000; 342 (18),pp 1334-1349
LINE COUNT: 00684 WORD COUNT: 09444

11/3,AB/26 (Item 3 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00118989

Mechanisms of Disease: Single-Gene Mutations Resulting in Reproductive Dysfunction in Women (Review Article)

Adashi, Eli Y.; Hennebold, Jon D.
The New England Journal of Medicine
Mar 4, 1999; 340 (9),pp 709-718
LINE COUNT: 00458 WORD COUNT: 06327

11/3,AB/27 (Item 4 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00116901

Medical Progress: Multiple Myeloma (Review Article)

Bataille, Regis; Harousseau, Jean-Luc.
The New England Journal of Medicine
Jun 5, 1997; 336 (23),pp 1657-1664
LINE COUNT: 00378 WORD COUNT: 05221

11/3,AB/28 (Item 5 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00113448

Drug Therapy: Histamine(sub 2)-Receptor **Antagonists** -- Standard Therapy For Acid-Peptic Diseases (First Of Two Parts) (Review Article)

Feldman, Mark; Burton, Michael E.
The New England Journal of Medicine
Dec 13, 1990; 323 (24),pp 1672-1680
LINE COUNT: 00419 WORD COUNT: 05792

11/3,AB/29 (Item 6 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00111836

Medical Progress: Progress In Psychiatry (Second of Two Parts) (Review Articles)

Michels, Robert; Marzuk, Peter M.
The New England Journal of Medicine
Aug 26, 1993; 329 (9),pp 628-638
LINE COUNT: 00799 WORD COUNT: 11032

11/3,AB/30 (Item 7 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00109586

Medical Progress: Recent Advances In Dermatology (Review Article)

Phillips, Tania J.; Dover, Jeffrey S.
The New England Journal of Medicine
Jan 16, 1992; 326 (3),pp 167-178
LINE COUNT: 00668 WORD COUNT: 09227

11/3,AB/31 (Item 8 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00108965

Medical Progress: Bacterial And Protozoal Gastroenteritis (Review Article)

Guerrant, Richard L.; Bobak, David A.
The New England Journal of Medicine
Aug 1, 1991; 325 (5),pp 327-340
LINE COUNT: 00741 WORD COUNT: 10238

11/3,AB/32 (Item 9 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00107713

Mechanisms of Disease: Leukotrienes And Other Products Of The 5-lipoxygenase Pathway -- Biochemistry And Relation To Pathobiology In **Human** Diseases (Review Article)

Lewis, Robert A.; Austen, K. Frank; Soberman, Roy J.
The New England Journal of Medicine
Sep 6, 1990; 323 (10),pp 645-655
LINE COUNT: 00668 WORD COUNT: 09219

11/3,AB/33 (Item 10 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00107236

Lasting Remissions In Hairy-Cell Leukemia Induced By A Single Infusion Of 2-Chlorodeoxyadenosine (Original Articles)

Piro, Lawrence D.; Carrera, Carlos J.; Carson, Dennis A.; Beutler,

Ernest.
The New England Journal of Medicine
Apr 19, 1990; 322 (16),pp 1117-1121
LINE COUNT: 00302 WORD COUNT: 04169

Abstract
2-Chlorodeoxyadenosine is a simple purine nucleoside that has previously been shown to be effective in the **treatment** of low-grade malignant disorders of lymphoid tissue, including chronic lymphocytic leukemia and non-Hodgkin's lymphoma. Because of these encouraging results, we **treated** 12 patients with another low-grade B-cell neoplasm, hairy-cell leukemia. The patients received 2-chlorodeoxyadenosine (0.1 mg per kilogram of body weight per day) by continuous infusion for seven days.

All the patients responded to **treatment**. Eleven had complete remissions characterized by the normalization of peripheral blood and bone marrow and disappearance of tumor masses. The longest remission has been 3.8 years. None of the patients have relapsed, and the median duration of remission has been 15.5 months. No serious toxic reactions occurred as a result of 2-chlorodeoxyadenosine therapy.

These results suggest that 2-chlorodeoxyadenosine may be the most effective therapy available for hairy-cell leukemia. The administration of 2-chlorodeoxyadenosine resulted in a higher rate of complete remission than is observed with interferon alfa, and it required no maintenance therapy. Its toxicity may be lower than that of deoxycoformycin, and the responses were achieved with single courses of **treatment**. (N Engl J Med 1990; 322:1117-21.)

11/3,AB/34 (Item 11 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00107182

Medical Progress: Acromegaly (Review Articles)

Melmed, Shlomo.
The New England Journal of Medicine
Apr 5, 1990; 322 (14),pp 966-977
LINE COUNT: 00736 WORD COUNT: 10169

11/3,AB/35 (Item 12 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00106303

Ethanol And The Nervous System (Medical Progress)

Charness, Michael E.; Simon, Roger P.; Greenberg, David A.
The New England Journal of Medicine
Aug 17, 1989; 321 (7),pp 442-454
LINE COUNT: 00878 WORD COUNT: 12129

11/3,AB/36 (Item 13 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00104396

The Role Of Thyroid-Stimulating Antibodies Of Graves' Disease In Differentiated Thyroid Cancer (Medical Intelligence)

Filetti, Sebastiano; Belfiore, Antonio; Amir, Syed M., Ph.D.; Daniels, Gilbert H.; Ippolito, Oracio; Vigneri, Riccardo; Ingbar, Sidney H.
The New England Journal of Medicine
March 24, 1988; 318 (12),pp 753-759
LINE COUNT: 00445 WORD COUNT: 06152
?


ds

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Set     Items   Description
S1       8018   CAMP
S2        528   S1 AND BR
S3         27   S2 AND (HIV OR AIDS OR CVI)
S4         26   RD (unique items)
? s s2 and (analog? or antagonist?)
             528  S2
          109321  ANALOG?
           99744  ANTAGONIST?
      S5     218  S2 AND (ANALOG? OR ANTAGONIST?)
? s s5 and (treat? or administer?)
             218  S5
          428589  TREAT?
           84626  ADMINISTER?
      S6     136  S5 AND (TREAT? OR ADMINISTER?)
? rd
>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
      S7     134  RD (unique items)
? s s7 and pka
             134  S7
            2036  PKA
      S8       7  S7 AND PKA
? t s8/3,ab/all
>>>No matching display code(s) found in file(s): 304

 8/3,AB/1     (Item 1 from file: 156)
DIALOG(R)File 156:ToxFile
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03004983   21458311   PMID: 11573967
  Inducible  RGS2  is  a  cross-talk  regulator  for  parathyroid  hormone
signaling in rat osteoblast-like UMR106 cells.
  Ko J K; Choi K H; Kim I S; Jung E K; Park D H
  Cancer Research Institute, Seoul National University College of Medicine,
28 Yungun-dong, Chongno-ku, Seoul 110-744, Korea. jaeguri@chollian.net
  Biochem  Biophys  Res  Commun (United  States)   Oct  5  2001,  287   (4)
 p1025-33,  ISSN 0006-291X   Journal Code: 0372516
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Parathyroid  hormone  (PTH)  activates  dual  signal  transduction  systems  via
Galphas  and  Galphaq  proteins.  We  now  report  a  novel  mechanism  by  which
"cross-talk"  may  occur  between  the  Galphas  and  Galphaq  signaling  pathways.
RGS2  (Regulator  of  G  protein  Signaling  2)  mRNA  was  rapidly  and  transiently
increased  only  by  PTH  analogs  (PTH1-84,  1-34,  1-31,  and  PTHrP)  that
activated  the  Galphas-mediated  cAMP/PKA  signaling  pathway,
whereas  activation  of  the  Galphaq-mediated  Ca(2+)/PKC  signaling  pathway  by
PTH3-34  had  no  effect  on  RGS2  expression.  Treatment  of  UMR106  cells
with  nonPTH  activators  of  the  cAMP/PKA  signaling  pathway  such
as  cholera  toxin,  forskolin,  8-Br-cAMP,  and  dibutyryl-
cAMP  also  significantly  elevated  RGS2  mRNA  levels,  while  activator  of
the  Galphaq  pathway  PMA  did  not.  Pretreatment  using  the  Galphas  signaling
pathway  inhibitors  SQ22536  and  H89  significantly  blocked  PTH-induced  RGS2
expression,  but  the  Galphaq  signaling  pathway  inhibitor  bisindolylmaleimide
I  had  no  effect.  Therefore,  RGS2  expression  is  governed  solely  by  the
Galphas  signaling  pathway.  Additionally,  we  demonstrate  for  the  first  time
```


that RGS2 binds to both Galphas and Galphaq subunits in their transition state (GDP/AlF(-4)-bound) forms, suggesting that RGS2 has the potential to act as a bridge between the **cAMP**/**PKA** and Ca(2+)/PKC pathways, and that it may act as a cross-talk regulator for these two PTH signaling pathways. Copyright 2001 Academic Press.

8/3,AB/2 (Item 2 from file: 156)
DIALOG(R)File 156:ToxFile
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01289191 99042108 PMID: 9822802
Dexamethasone rapidly regulates TRH mRNA levels in hypothalamic cell cultures: interaction with the **cAMP** pathway.
Perez-Martinez L; Carreon-Rodriguez A; Gonzalez-Alzati M E; Morales C; Charli J L; Joseph-Bravo P
Departamento de Genetica y Fisiologia Molecular, Instituto de Biotecnologia, Universidad Nacional Autonoma de Mexico, Cuernavaca, Mexico.
Neuroendocrinology (SWITZERLAND) Nov 1998, 68 (5) p345-54, ISSN 0028-3835 Journal Code: 0035665
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The biosynthesis of thyrotropin-releasing hormone (TRH) in the hypothalamic paraventricular nucleus (PVN) is subject to neural and hormonal regulations. To identify some of the potential effectors of this modulation, we incubated hypothalamic dispersed cells with dexamethasone for short periods of time (1-3 h) and studied the interaction of this hormone with protein kinase C (PKC) and **PKA** signaling pathways. TRH mRNA relative changes were determined by the RT-PCR technique. One hour incubation with 10(-10)-10(-4) M dexamethasone produced a concentration-dependent biphasic effect: an inhibition was observed on TRH mRNA levels at 10(-10) M, an increase above control at 10(-8)-10(-6) M and a reduction at higher concentrations (10(-5)- 10(-4) M). The stimulatory effect of 10(-8) M dexamethasone on TRH mRNA was essentially independent of new protein synthesis, as evidenced by cycloheximide pretreatment. Changes in TRH mRNA levels were reflected by enhanced TRH cell content. Incubation with a **cAMP analogue** (8-bromo-**cAMP**, 8Br-**cAMP**) or with a PKC activator (12-O-tetradecanoylphorbol-13-acetate, TPA) increased TRH mRNA levels after 1 and 2 h, respectively. An increase in TRH mRNA expression was observed by in situ hybridization of dexamethasone or 8Br-**cAMP-treated** cells. The interaction of dexamethasone, **PKA** and PKC signaling pathways was studied by combined **treatment**. The stimulatory effect of 10(-7) M TPA on TRH mRNA levels was additive to that of dexamethasone; in contrast, coincubation with 10(-3) M 8-**Br-cAMP** and dexamethasone diminished the stimulatory effect of both drugs. An inhibition was observed when the **cAMP analogue** was coincubated with TPA or TPA and dexamethasone. These results demonstrate that dexamethasone can rapidly regulate TRH biosynthesis and suggest a cross talk between **cAMP**, glucocorticoid receptors and PKC transducing pathways.

8/3,AB/3 (Item 3 from file: 156)
DIALOG(R)File 156:ToxFile
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01247420 98217028 PMID: 9557948
Effect of PGE2 on the cell surface molecule expression in PMA **treated** thymocytes.
Daculsi R; Vaillier D; Carron J C; Gualde N
CNRS UMR 5540, Universite Victor Segalen Bordeaux 2, France.
Immunology letters (NETHERLANDS) Feb 1998, 60 (2-3) p81-8, ISSN

0165-2478 Journal Code: 7910006
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

PGE2 is produced by cells of the thymic microenvironment. The effects of PGE2 are mediated by **cAMP** through binding to its intracellular receptor protein kinase A (**PKA**). Phorbol 12-myristate 13-acetate (PMA) is known to modulate CD molecule expression on thymocytes, probably through activation of protein kinase C (PKC). We have hypothesized that cross-talk between these two signalling pathways may affect modulation of the CD molecules on the cell surface of thymocytes. For this purpose, we compare the effects of PMA alone or combined with PGE2 on CD3, CD4 and CD8 expression on mouse thymocytes by flow-cytometric analysis. PMA **treatment** almost completely abolished CD4 expression and slightly decreased CD3 and CD8 expression. PGE2 alone did not change the CD3, CD4 and CD8 molecule expression. Combined with PMA, PGE2 can overcome the decrease induced by PMA of the CD3 expression and partially reduced the disappearance of the CD4 molecule. On the other hand PGE2 accelerated the loss of CD8 molecule expression. These events occurred only in CD4+ CD8+ immature thymocytes. An **analogue** of **cAMP** (dibutyryl **cAMP**) mimics the effect of PGE2, but not **Br** -cGMP. This differential regulation by PGE2 of the CD molecule expression on immature thymocytes may provide additional evidence on the role of PGE2 during the process of thymic differentiation.

8/3,AB/4 (Item 4 from file: 156)
DIALOG(R)File 156:ToxFile

01179174 97190271 PMID: 9038153
Selective activation of **cAMP** -dependent protein kinase type I inhibits rat natural killer cell cytotoxicity.
Torgersen K M; Vaage J T; Levy F O; Hansson V; Rolstad B; Tasken K
Department of Anatomy, Institute of Basic Medical Sciences, University of Oslo, N-0317 Oslo, Norway. k.m.torgersen@basalmed.uio.no
Journal of biological chemistry (UNITED STATES) Feb 28 1997, 272 (9) p5495-500, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The present study examines the expression and involvement of **cAMP** -dependent protein kinase (**PKA**) isozymes in **cAMP** -induced inhibition of natural killer (NK) cell-mediated cytotoxicity. Rat interleukin-2-activated NK cells express the **PKA** alpha-isoforms RIalpha, RIIalpha, and Calpha and contain both **PKA** type I and type II. Prostaglandin E2, forskolin, and **cAMP analogs** all inhibit NK cell lysis of major histocompatibility complex class I mismatched allogeneic lymphocytes as well as of standard tumor target cells. Specific involvement of **PKA** in the **cAMP**-induced inhibition of NK cell cytotoxicity is demonstrated by the ability of a **cAMP antagonist**, (Rp)-8-**Br**-adenosine 3',5'-cyclic monophosphorothioate, to reverse the inhibitory effect of complementary **cAMP** agonist (Sp)-8-**Br** -adenosine 3',5'-cyclic monophosphorothioate. Furthermore, the use of **cAMP analog** pairs selective for either **PKA** isozyme (**PKA** type I or **PKA** type II), shows a preferential involvement of the **PKA** type I isozyme, indicating that **PKA** type I is necessary and sufficient to completely abolish killer activatory signaling leading to NK cell cytotoxicity. Finally, combined **treatment** with phorbol ester and ionomycin maintains NK cell cytotoxicity and eliminates the **cAMP** -mediated inhibition, demonstrating that protein kinase C and Ca2+-dependent events stimulate the

cytolytic activity of NK cells at a site distal to the site of **cAMP**/**PKA** action.

8/3,AB/5 (Item 5 from file: 156)
DIALOG(R)File 156:ToxFile

01170872 97123701 PMID: 8968948
Deletion of the N-terminus of a K+ channel brings about short-term modulation by **cAMP** and beta 1-adrenergic receptor activation.
Levin G; Peretz T; Chikvashvilli D; Jing J; Lotan I
Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Israel.
Journal of molecular neuroscience : MN (UNITED STATES) Winter 1996, 7 (4) p269-76, ISSN 0895-8696 Journal Code: 9002991
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
On deletion of the N-terminus of RCK1 K+ channel, acute modulation of the channel by **cAMP**-elevating **treatments** is revealed. This modulation is studied in Xenopus oocytes using two-electrode voltage-clamp, site-directed mutagenesis, and SDS-PAGE analyses. **Treatments** by Sp-8-**Br**-cAMPS, a membrane-permeant **cAMP analog** , and by isoproterenol, a beta 1-adrenergic receptor (beta 1R) agonist, both increased the current amplitudes with no effect on the voltage dependency of activation. The effect of isoproterenol was blocked by coexpression of either G alpha S or G alpha i3 proteins. The channel protein is phosphorylated on the Sp-8-**Br**-cAMPS **treatment** at Ser446; however, a phosphorylation-deficient variant in which this site has been altered is still modulated by Sp-8-**Br** -cAMPS and isoproterenol. Expression of the full-length channel with Kv beta 1.1 auxiliary subunit renders the channel at the same modulation as that of the truncated one. Taken together, the RCK1 channel can be acutely modulated by **cAMP** and beta 1R activation possibly through protein kinase A (**PKA**) activation, but not through direct channel phosphorylation; the involvement of the N-terminus in this modulation is discussed.

8/3,AB/6 (Item 6 from file: 156)
DIALOG(R)File 156:ToxFile

01107515 96141205 PMID: 8559283
Modulation of regulatory and catalytic subunit levels of **cAMP** -dependent protein kinase A in anterior pituitary cells in response to direct activation of protein kinases A and C or after GnRH stimulation.
Garrel G; Delahaye R; Hemmings B A; Counis R
Endocrinologie Cellulaire et Moleculaire de la Reproduction, URA CNRS 1449, Universite Pierre et Marie Curie, France.
Neuroendocrinology (SWITZERLAND) Nov 1995, 62 (5) p514-22, ISSN 0028-3835 Journal Code: 0035665
Erratum in Neuroendocrinology 1996 Feb;63(2) 187
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have previously shown that direct activation of protein kinase A (**PKA**) and protein kinase C (PKC) induced changes in the expression of genes coding for **PKA** RII beta and C alpha subunit isoforms in cultured anterior pituitary cells, suggesting the possibility of interconnected regulation at this point. To evaluate whether the cell content of **PKA** protein subunits could be similarly altered, the

catalytic (C) and regulatory type I (RI) and type II (RII) subunits were identified by Western blot analysis using specific immunoaffinity-purified antibodies. Activation of **PKA** by the permeant cyclic adenosine monophosphate (**cAMP**) **analogue** 8-**Br**-**cAMP** induced a dramatic time- and concentration-dependent decline of C subunit to a residual level that may represent 10-15% of that in untreated cells. The most profound decrease occurred during the first 5 h following **treatment** with 0.5-2 mM **analogue** (by 65 +/- 14 and 79 +/- 5%, respectively). Under identical conditions, RII was increased by about 40% at the higher concentrations, while RI increased slightly, but only at low concentrations (below 1 mM 8-**Br**-**cAMP**), and then gradually decreased. Exposure of cells to the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) also resulted in decreased levels of the **PKA** C subunit, however, with a different concentration-dependent profile. In particular, a decline in **PKA** C was most pronounced (60%) at a low concentration of TPA (10 nM) as compared with the concentrations equal to or above 20 nM (40% decrease). TPA at 10 nM also depressed notably (by 25%) the level of RII subunit, but higher concentrations were essentially ineffective, although a slight and statistically not significant elevation of the cell subunit content was observed as for RI. Simultaneous activation of both **PKA** and PKC pathways resulted in further depletion of **PKA** C and an important loss (50%) of RII, a subunit which was enhanced by the activation of either system alone. Finally, gonadotropin-releasing hormone, a neuropeptide that has the potentiality to activate both **PKA** and PKC signaling in gonadotropes, was able to alter **PKA** subunit cell content: **PKA** C was significantly reduced at either a subliminal (0.1 nM) or maximal (10 nM) concentration, whereas RII increased at the low concentration and decreased at the high concentration. In conclusion, these data demonstrate that the pituitary cell contents of RI, RII, and C subunits of **PKA** are regulated under the activation of **PKA** itself as well as PKC in a manner that can exhibit further alteration when both systems come simultaneously into play. Changes in the **PKA** subunit levels in certain cases may correlate with a variation of the mRNAs suggesting multiple control mechanisms, including an alteration of gene expression and changes in subunit degradation, synthesis, and/or turnover. These data, together with those obtained in the presence of gonadotropin-releasing hormone, provide further support for a hormonally induced interplay between **PKA** and PKC signaling pathways at the crucial level of **PKA** in the pituitary gland including gonadotropes.

00110607

Medical Progress: The Pathogenesis And **Treatment** Of Kidney Stones (Review Article)

Coe, Fredric L.; Parks, Joan H.; Asplin, John R.
The New England Journal of Medicine
Oct 15, 1992; 327 (16),pp 1141-1152
LINE COUNT: 00687 WORD COUNT: 09482

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4/3,AB/1 (Item 1 from file: 156)
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01295532 99113788 PMID: 9916750
Increased activation of protein kinase A type I contributes to the T cell deficiency in common variable immunodeficiency.
Aukrust P; Aandahl E M; Skalhegg B S; Nordoy I; Hansson V; Tasken K; Froland S S; Muller F
Research Institute for Internal Medicine, Medical Department A, Rikshospitalet, Oslo, Norway. pal.aukrust@klinmed.uio.no
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jan 15 1999, 162 (2) p1178-85, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The molecular mechanisms underlying the T cell dysfunction often present in common variable immunodeficiency (**CVI**) are not established. **cAMP** -dependent protein kinase A type I (PKAI) is an important inhibitor of T cell proliferation after Ag stimulation. We therefore investigated the possibility that activation of PKAI may be involved in the development of T cell dysfunction in **CVI** . An exogenously added PKAI-selective antagonist (Rp-8-**Br** -cAMPS) induced a significant increase in anti-CD3-stimulated PBMC proliferation in 20 **CVI** patients compared with no effect in 15 controls. Purified T cells from 7 **CVI** patients with strictly defined T cell deficiency had elevated endogenous **cAMP** levels compared with controls. Treatment of T cells from these

CVI patients with Rp-8-bromo-**cAMP** -phosphorothioate markedly improved anti-CD3-stimulated proliferation (up to 3.7-fold), particularly in CD4+ lymphocytes, reaching proliferation levels comparable to control values. No effect of **cAMP** antagonist on T cell proliferation was seen in controls. In these **CVI** patients, **cAMP** antagonist also increased IL-2 production in anti-CD3-stimulated T cells. However, exogenously added IL-2 at concentrations comparable to the achieved increase in IL-2 levels after addition of **cAMP** antagonist had no effect on T cell proliferation. Furthermore, the stimulatory effects of exogenously added IL-2 at higher concentrations and **cAMP** antagonist on T cell proliferation were additive. Our findings indicate that increased PKAI activation may be an important molecular basis for the T cell defect in **CVI** and suggest that the **cAMP**/PKAI system may be a potential molecular target for immunomodulating therapy in these patients.

4/3,AB/2 (Item 1 from file: 442)
DIALOG(R)File 442:AMA Journals

00117484

Herbal Medicines and Perioperative Care (ARTICLE)

ANG-LEE, MICHAEL K. Jonathan Moss, MD, PhD Chun-Su Yuan, MD, PhD
JAMA, The Journal of the American Medical Association
July 11, 2001; 2: tzj208
LINE COUNT: 00896

4/3,AB/3 (Item 2 from file: 442)
DIALOG(R)File 442:AMA Journals

00114366

Autonomic Performance and Dehydroepiandrosterone Sulfate Levels in **HIV** -1-Infected Individuals Relationship to TH/1 and TH/2 Cytokine Profile (ARTICLE)

SCHIFITTO, GIOVANNI; MCDERMOTT, MICHAEL P.; EVANS, THOMAS; FITZGERALD, THERESA; SCHWIMMER, JOSHUA; DEMETER, LISA; KIEBURTZ, KARL
Archives of Neurology
July, 2000; Original: tzn1027
LINE COUNT: 00513

Background: Products of immune activation, including cytokines and lipid membrane derivatives, have been implicated in the pathogenesis of the neurologic sequelae, including autonomic dysfunction, associated with human immunodeficiency virus 1 (**HIV** -1) infection. In animal models, autonomic and endocrine dysfunction are associated with an altered cytokine profile. Objectives: To investigate the relationship between markers of immune activation (B2/-microglobulin), **HIV** -1 disease progression (CD4/+/ cell count and viral load), and autonomic nervous system performance and to assess the relationship between autonomic performance, plasma levels of dehydroepiandrosterone sulfate (DHEAS), and TH/1 and TH/2 cytokine profile. Methods: Thirty-one **HIV**-1-infected individuals and 22 **HIV** -1-negative controls were evaluated with a comprehensive neurologic, neuropsychological, and autonomic examination. Interleukin 4 and interferon gamma were measured by enzyme-linked immunosorbent assay in the supernatant of stimulated peripheral blood mononuclear cells. Results: A composite measure of autonomic performance (AZ score) was significantly

lower (worse autonomic function) in patients compared with controls (P=.04). A lower AZ score was associated with higher B2/-microglobulin serum levels and a lower CD4/+/ cell count. Interleukin 4 levels were significantly inversely associated with AZ score (P=.01), whereas interferon gamma levels were significantly positively associated with DHEAS levels (P=.04). Conclusions: Our data show significant associations between markers of immune activation and disease progression and a composite measure of autonomic function in **HIV** -1-infected individuals. In addition, they suggest that poor autonomic function and low DHEAS plasma levels tend to be associated with an unbalanced cytokine profile. Arch Neurol. 2000;57:1027-1032

4/3,AB/4 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals

00109024

Postexposure Prophylaxis After Nonoccupational **HIV** Exposure Clinical, Ethical, and Policy Considerations (ARTICLE)

LURIE, PETER; MILLER, SUELLEN; HECHT, FREDERICK; CHESNEY, MARGARET; LO, BERNARD
JAMA, The Journal of the American Medical Association
November 25, 1998; 20: tzj1769
LINE COUNT: 00615

In the wake of recent breakthroughs in antiviral therapies and Centers for Disease Control and Prevention (CDC) recommendations advocating occupational postexposure prophylaxis (PEP), health care workers are increasingly receiving inquiries about PEP following exposures to the human immunodeficiency virus (**HIV**) through sex and injection drug use. The probability of **HIV** transmission by certain sexual or injection drug exposures is of the same order of magnitude as percutaneous occupational exposures for which the CDC recommends PEP. In such cases, if the exposure is sporadic, it seems appropriate to extrapolate from the data on occupational PEP and recommend prophylaxis. However, for individuals with continuing or low-risk exposures, we instead recommend referrals to state-of-the-art risk reduction programs. Clinicians, using local **HIV** seroprevalence data and their knowledge of transmission probabilities, can help exposed patients make an informed decision regarding PEP. Because of the large number of risky encounters that will not be treated prophylactically, even after significant outreach efforts, public health interventions that emphasize PEP as part of a comprehensive **HIV** prevention program should be confined to cities with highest **HIV** prevalences.JAMA. 1998;280:1769-1773

4/3,AB/5 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals

00108542

Effects of Computer-Based Clinical Decision Support Systems on Physician Performance and Patient Outcomes A Systematic Review (ARTICLE)

HUNT, DERECK L.; HAYNES, R. BRIAN; HANNA, STEVEN E.; SMITH, KRISTINA
JAMA, The Journal of the American Medical Association
October 21, 1998; 15: tzj1339
LINE COUNT: 00681

Context.--Many computer software developers and vendors claim that their systems can directly improve clinical decisions. As for other health care interventions, such claims should be based on careful trials that assess their effects on clinical performance and, preferably, patient outcomes. Objective.--To systematically review controlled clinical trials assessing the effects of computer-based clinical decision support systems (CDSSs) on physician performance and patient outcomes. Data Sources.--We updated earlier reviews covering 1974 to 1992 by searching the MEDLINE, EMBASE, INSPEC, SCISEARCH, and the Cochrane Library bibliographic databases from 1992 to March 1998. Reference lists and conference proceedings were reviewed and evaluators of CDSSs were contacted. Study Selection.--Studies were included if they involved the use of a CDSS in a clinical setting by a health care practitioner and assessed the effects of the system prospectively with a concurrent control. Data Extraction.--The validity of each relevant study (scored from 0-10) was evaluated in duplicate. Data on setting, subjects, computer systems, and outcomes were abstracted and a power analysis was done on studies with negative findings. Data Synthesis.--A total of 68 controlled trials met our criteria, 40 of which were published since 1992. Quality scores ranged from 2 to10, with more recent trials rating higher (mean, 7.7) than earlier studies (mean, 6.4) (P<.001). Effects on physician performance were assessed in 65 studies and 43 found a benefit (66%). These included 9 of 15 studies on drug dosing systems, 1 of 5 studies on diagnostic **aids**, 14 of 19 preventive care systems, and 19 of 26 studies evaluating CDSSs for other medical care. Six of 14 studies assessing patient outcomes found a benefit. Of the remaining 8 studies, only 3 had a power of greater than 80% to detect a clinically important effect. Conclusions.--Published studies of CDSSs are increasing rapidly, and their quality is improving. The CDSSs can enhance clinical performance for drug dosing, preventive care, and other aspects of medical care, but not convincingly for diagnosis. The effects of CDSSs on patient outcomes have been insufficiently studied.JAMA. 1998;280:1339-1346 From the Graduate Program in Health Research Methodology (Dr Hunt), the Health Information Research Unit, Department of Clinical Epidemiology and Biostatistics (Drs Hunt, Haynes, and Hanna and Ms Smith), and the Department of Medicine (Drs Hunt and Haynes), McMaster University Faculty of Health Sciences, Hamilton, Ontario.

4/3,AB/6 (Item 5 from file: 442)
DIALOG(R)File 442:AMA Journals

00106723

Directly Observed Therapy for Treatment Completion of Pulmonary Tuberculosis Consensus Statement of the Public Health Tuberculosis Guidelines Panel (ARTICLE)

CHAULK, C. PATRICK; KAZANDJIAN, VAHE A.; PANEL, FOR THE PUBLIC HEALTH TUBERCULOSIS GUIDELINES
JAMA, The Journal of the American Medical Association
March 25, 1998; 12: tzj943
LINE COUNT: 00549

Objective.--To evaluate evidence on the relative effectiveness of directly observed therapy in achieving treatment completion for pulmonary tuberculosis. Participants.--A panel of 11 practitioners representing the public health, behavioral, and clinical management of tuberculosis was convened by the Council on Linkages Between Academia and Public Health Practice in 1995 to develop public health guidelines for tuberculosis treatment completion. Evidence.--English-language articles identified through MEDLINE (1966 to August 1, 1996) with original data on directly

observed therapy, supervised therapy, compliance, treatment completion, case management, and treatment adherence for tuberculosis. Consensus Process.--Each eligible article underwent structured review by at least 2 panel members for study design, sample size, evaluation methods, and treatment completion as the primary outcome. The full panel was convened twice, with intercurrent small group meetings, conference calls, and summary workshop to review findings. Recommendations made through this process were drafted by the panel chair and circulated twice for additional panel comments. Conclusions.--Treatment completion rates for pulmonary tuberculosis are most likely to exceed 90%, as recommended by the Centers for Disease Control and Prevention, when treatment is based on a patient-centered approach using directly observed therapy with multiple enablers and enhancers. Other less intensive interventions, including nonsupervised strategies and modified approaches to directly observed therapy, are unlikely to achieve this recommended treatment completion goal. Directly observed therapy also appears to be cost-effective compared with self-administered therapy, although data on cost-effectiveness are limited. JAMA. 1998;279:943-948

4/3,AB/7 (Item 6 from file: 442)
DIALOG(R)File 442:AMA Journals

00106064

Association of an HLA-DQ Allele With Clinical Tuberculosis (ARTICLE)

GOLDFELD, ANNE E.; DELGADO, JULIO C.; THIM, SOK; BOZON, M. VIVIANA; UGLIALORO, ADELE M.; TURBAY, DAVID; COHEN, CAROL; YUNIS, EDMOND J.
JAMA, The Journal of the American Medical Association
January 21, 1998; 3: tzj226
LINE COUNT: 00329

Context.--Although tuberculosis (TB) is the leading worldwide cause of death due to an infectious disease, the extent to which progressive clinical disease is associated with genetic host factors remains undefined. Objective.--To determine the distribution of HLA antigens and the frequency of 2 alleles of the tumor necrosis factor <unprintable> (TNF-<unprintable>) gene in unrelated individuals with clinical TB (cases) compared with individuals with no history of clinical TB (controls) in a population with a high prevalence of TB exposure. Design.--A 2-stage, case-control molecular typing study conducted in 1995-1996. Setting.--Three district hospitals in Svay Rieng Province in rural Cambodia. Patients.--A total of 78 patients with clinical TB and 49 controls were included in the first stage and 48 patients with TB and 39 controls from the same area and socioeconomic status were included in the second stage. Main Outcome Measures.--Presence of HLA class I and class II alleles determined by sequence-specific oligonucleotide probe hybridization and presence of 2 TNF-<unprintable> alleles determined by restriction fragment length polymorphism analysis. Results.--In the first stage, 7 DQB10503 alleles were detected among 156 alleles derived from patients with TB, whereas no DQB10503 alleles were found among the 98 alleles derived from controls (P=.04). There was no detectable difference in the distribution of the 2 TNF-<unprintable> alleles in patients with TB compared with controls. In the second stage, we tested for the presence of a single variable, the DQB10503 allele, and found 9 DQB10503 alleles among 96 alleles derived from patients with TB and no DQB10503 alleles among 78 alleles in controls (P=.005). Conclusions.--The HLA-DQB10503 allele is significantly associated with susceptibility to TB in Cambodian patients and, to our knowledge, is the first identified gene associated with development of clinical TB. JAMA. 1998;279:226-228

4/3,AB/8 (Item 7 from file: 442)
DIALOG(R)File 442:AMA Journals

00102942

Penciclovir Cream for the Treatment of Herpes Simplex Labialis A Randomized, Multicenter, Double-blind, Placebo-Controlled Trial (ARTICLE)

SPRUANCE, SPOTSWOOD L.; REA, TED L.; THOMING, CHRISTOPHER; TUCKER, RICHARD; SALTZMAN, ROBIN; BOON, RON; GROUP, FOR THE TOPICAL PENCICLOVIR COLLABORATIVE STUDY
JAMA, The Journal of the American Medical Association
May 7, 1997; 17: tzj1374
LINE COUNT: 00598

Objective.--To compare the safety and efficacy of topical 1% penciclovir cream with vehicle control cream (placebo) for the treatment of a recurrent episode of herpes simplex labialis (cold sores) in immunocompetent patients. Design.--Randomized, double-blind, placebo-controlled, patient-initiated, 2-armed, parallel clinical trial. Patients were prospectively dispensed study medication, and treatment was self-initiated by the patient within 1 hour of the first sign or symptom of a recurrence. Setting.--A total of 31 ambulatory clinics in the United States in a variety of settings, including private practices, public health facilities, and universities. Patients.--Otherwise healthy individuals with a history of frequentepisodes of herpes simplex labialis. A total of 2209 patients were enrolled and given study medication, and 1573 initiated treatment fora recurrence. Interventions.--Topical 1% penciclovir cream or vehicle control cream. Subjects applied treatment every 2 hours while awake for 4 consecutive days. Main Outcome Measures.--Lesion healing was the primary efficacy variable. Secondary end points included time to loss of lesion pain and time to cessation of viral shedding. Results.--Healing of classical lesions (vesicles, ulcers, and/or crusts) was 0.7 day faster for penciclovir-treated patients compared with those who received vehicle control cream (median, 4.8 days vs 5.5 days; hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.18-1.49; P<.001). Pain (median, 3.5 days vs 4.1 days; HR, 1.22; 95%CI, 1.09-1.36; P<.001) and lesion virus shedding (median, 3 days vs 3days; HR, 1.35; 95% CI, 1.10-1.64; P=.003) also resolved more quicklyfor penciclovir-treated patients compared with patients who applied the vehicle control. The efficacy of penciclovir cream was apparent when therapy was initiated early (prodrome or erythema lesion stage) and when initiated late (papule or vesicle stage). The incidence of adverse events was comparable between penciclovir and placebo groups. Conclusions.--Penciclovir cream is the first treatment to clearly demonstrate an impact on the course of recurrent herpes labialis in immunocompetent patients. Efficacy was seen in all clinical and laboratory measures of the disease (lesion healing, pain resolution, and cessation of viral shedding). Faster healing and pain resolution occurred both among patients who first applied penciclovir cream in the prodrome and erythema stages and among those who started treatment in the papule and vesicle lesion stages.JAMA. 1997;277:1374-1379

4/3,AB/9 (Item 8 from file: 442)
DIALOG(R)File 442:AMA Journals

00101637

Genocide and the Plight of Children in Rwanda (ARTICLE)

GELTMAN, PAUL; STOVER, ERIC
JAMA, The Journal of the American Medical Association
January 22/29, 1997; 4: tzj289
LINE COUNT: 00713

4/3,AB/10 (Item 9 from file: 442)
DIALOG(R)File 442:AMA Journals

00101282

Transforming Growth Factor-B1 Inhibits Synthesis of Cytokines in Endotoxin-Stimulated Human Whole Blood (ARTICLE)

KARRES, INA; KREMER, JEAN-PIERRE; STECKHOLZER, URSULA; KENNEY, JOHN S.; ERTEL, WOLFGANG
Archives of Surgery
Dec, 1996; Paper: tzs1310
LINE COUNT: 00573

Objective: To determine the potency of transforming growth factor-B (TGF-B) for inhibiting proinflammatory cytokine synthesis in endotoxin-stimulated human whole blood. Design: Endotoxin-stimulated whole blood from healthy volunteers asan ex vivo model of endotoxemia was incubated with different concentrations of TGF-B1. Cytokine levels in plasma with a bioassay (for tumor necrosis factor <unprintable>) or an enzyme-linked immunosorbent assay (for interleukin [IL]-1B and IL-6), messenger RNA(mRNA) expression with northern blotting, and protein levels with Western blotting were determined. Results: High TGF-B1 concentrations (>100 pg/mL) inhibited (P<.05) secretion of tumor necrosis factor <unprintable>, IL-1B, and IL-6 into lipopolysaccharide-stimulated whole blood, while low concentrations (<50 pg/mL) were ineffective. Moreover, TGF-B1 inhibited mRNA expression of tumor necrosis factor <unprintable> and IL-6 in a dose-dependent manner. In contrast, neither IL-1B mRNA expression nor IL-1B protein synthesis were attenuated by TGF-B1. Conclusion: Transforming growth factor-B1, with its downregulatory effect on the synthesis and release of proinflammatory cytokines by phagocytic cells, represents an inhibitor of endotoxin-induced inflammatory reactions. Arch Surg. 1996;131:1310-1317

4/3,AB/11 (Item 10 from file: 442)
DIALOG(R)File 442:AMA Journals

00097918

Biotherapeutic Agents A Neglected Modality for the Treatment and Prevention of Selected Intestinal and Vaginal Infections (ARTICLE)

ELMER, GARY W.; SURAWICZ, CHRISTINA M.; MCFARLAND, LYNNE V.
JAMA, The Journal of the American Medical Association
March 20, 1996; 11: tzj870
LINE COUNT: 00810

Objective.--To evaluate the potential of biotherapeutic agents (microorganisms with therapeutic properties) for the prevention and/or treatment of selected intestinal and vaginal infections. Data Sources.--The MEDLINE database was searched for all relevant articles published between 1966 and September 1995. Search terms usedwere

biotherapeutic agent, probiotic, Lactobacillus, Saccharomyces, Bifidobacterium, Candida, gastrointestinal-system, vaginitis, vaginosis-bacterial, and related terms. The bibliographies of obtained articles were also reviewed. Study Selection and Data Extraction.--All placebo-controlled human studies on biotherapeutic agents were reviewed. English-language opentrials, case series and reports, and animal studies were reviewed only if they were especially relevant to providing information on thepotential efficacy, adverse effects, or mechanisms of action of theseagents. Data Synthesis.--Placebo-controlled studies have shown that biotherapeutic agents have been used successfully to prevent antibiotic-associated diarrhea (Lactobacillus casei GG, Bifidobacterium longum, B longum with L acidophilus, and Saccharomyces boulardii), to prevent acute infantile diarrhea (Bifidobacterium bifidum with Streptococcus thermophilus), to treat recurrent Clostridium difficile disease (S boulardii), and to treat various other diarrheal illnesses (Enterococcus faecium SF68, L caseiGG, and S boulardii). There is also limited evidence for Lactobacillus acidophilus in the prevention of candidal vaginitis. Few adverse effects have been reported. However, many of the studies tested only small numbers of patients or volunteers. Conclusions.--There is now evidence that administration of selectedmicroorganisms is beneficial in the prevention and treatment of certain intestinal and, possibly, treatment of vaginal infections. Inan effort to decrease the reliance on antimicrobials, the time has come to carefully explore the therapeutic applications of biotherapeutic agents.(JAMA. 1996;275:870-876) From the Department of Medicinal Chemistry, School of Pharmacy (Drs Elmer and McFarland), and the Division of Gastroenterology, Department of Medicine, School of Medicine (Dr Surawicz), University of Washington, Seattle.

4/3,AB/12 (Item 11 from file: 442)

00097913

Malacoplakia Two Case Reports and a Comparison of Treatment Modalities Based on a Literature Review (ARTICLE)

VAN DER VOORT, PETER H. J.; VELDEN, JOS J. A. M. TEN; WASSENAAR, RONALD P.; SILBERBUSCH, JOSEPH
Archives of Internal Medicine
Mar 11,, 1996; Clinical Observation: tzi577
LINE COUNT: 00666

Malacoplakia is a rare infectious disease that has been almost exclusively reported in urology and pathology journals. We studied two cases of malacoplakia that were primarily referred to the department of internal medicine because of fever and abdominal masses. In one patient, malacoplakia was diagnosed in the unusual ovarian location, while in the other patient a large renal mass was found and ciprofloxacin therapy failed because of bacterial resistance. The clinical and radiologic appearance of malacoplakia often mimics that of a malignant tumor. The principal disorder is probably a monocytic-macrophagic bactericidal defect. A definitive diagnosis depends on microscopic detection of Michaelis-Gutmann bodies by means of von Kossa stain. We outlined treatment strategies on the basis of a review of the literature since 1981, which included140 cases. If possible, immunosuppressive drugs should be stopped. Quinolone antibiotic treatment and surgical excision or incision and drainage lead to the highest cure rates (90% and 81%, respectively). Specific intracellular penetration of quinolone antibiotics is a possible reason for the higher cure rate achieved with these antibiotics. Bethanechol has been suggested to correct the supposed fundamental disturbance by increasing the

intracellular cyclic guanosine monophosphate concentration, but there is still no convincing evidence of its clinical efficacy. (Arch Intern Med. 1996;156:577-583)

4/3,AB/13 (Item 12 from file: 442)
DIALOG(R)File 442:AMA Journals

00095147

Superantigens Do They Have a Role in Skin Diseases? (ARTICLE)

SKOV, LONE
Archives of Dermatology
July, 1995; Review Article: de_829
LINE COUNT: 00333

Superantigens are a group of bacterial and viral proteins that are characterized by their capacity to stimulate a large number of T cells. They bind directly to the major histocompatibility complex class II molecule on the antigen-presenting cell and cross-link the antigen-presenting cell with T cells expressing certain T-cell receptors, leading to polyclonal T-cell activation. They have been shown to play a role in toxic shock syndrome and mucocutaneous lymph node syndrome and are postulated to play a role in other systemic diseases. Because inflammatory skin diseases such as atopic dermatitis and psoriasis are often known to be colonized with superantigen-releasing Staphylococcus aureus, the role of superantigens in skin diseases is of major importance. Recent studieshave demonstrated that if a staphylococcal superantigen is applied onintact human skin, a clinical picture of dermatitis evolves. Furthermore, in the presence of superantigens, epidermal cells potently activate T cells. Thus, superantigens may play a role in theinduction and exacerbation of inflammatory skin diseases. (Arch Dermatol. 1995;131:829-832)

4/3,AB/14 (Item 13 from file: 442)
DIALOG(R)File 442:AMA Journals

00090568

Bilateral B2/-Microglobulin Amyloidomas of the Buttocks in a Long-term Hemodialysis Patient (ARTICLE)

Archives of Pathology and Laboratory Medicine
June, 1994; Brief: pt_651
LINE COUNT: 01390

Only two cases of B2/-microglobulin amyloid tumors involving the buttocks have been reported in the world literature. We report a caseof bilateral buttock amyloid tumors with associated carpal tunnel syndrome and pathologic fracture involving the femoral head. This unusual local bilateral manifestation of the B2/-microglobulin amyloidosis develops late in the course of hemodialysis and may be initiated by chronic trauma. (Arch Pathol Lab Med. 1994;118:651-653)

4/3,AB/15 (Item 14 from file: 442)
DIALOG(R)File 442:AMA Journals

00089173

Infectious Diseases in Competitive Sports (ARTICLE)

JAMA, The Journal of the American Medical Association
March 16, 1994; 11: p862
LINE COUNT: 00563

Objective.--Participation in competitive sports is popular and widelyencouraged throughout the United States. Reports of infectious disease outbreaks among competitive athletes and recent publicity regarding infectious disease concerns in sports underscore the need to better characterize the occurrence of these problems. Data Sources.--To identify reports of infectious diseases in sports, we performed a comprehensive search of the medical literature(MEDLINE) and newspaper databases in two on-line services (NEXIS and DIALOG PAPERS). Study Selection.--Articles selected from the literature review included those describing cases or outbreaks of disease in which exposure to an infectious agent was likely to have occurred during training for competitive sports or during actual competition. Articles from the newspaper review included reports of outbreaks, exposures, or preventive measures that directly or indirectly involved teams or spectators. Data Synthesis.--The literature review identified 38 reports of infectious disease outbreaks or other instances of transmission through person-to-person (24 reports), common-source (nine reports), or airborne (five reports) routes; the newspaper search identified 28reports. Infectious agents included predominantly viruses but also a variety of fungi and gram-positive and gram-negative bacteria. Conclusions.--Our findings indicate that strategies to prevent transmission of infectious diseases in sports must recognize risks atthree levels: the individual · athlete, the team, and spectators or others who may become exposed to infectious diseases as a result of sports-related activities. Team physicians and others who are responsible for the health of athletes should be especially familiar with the features of infectious diseases that occur in sports and measures for the prevention of these problems. (JAMA. 1994;271:862-867)

4/3,AB/16 (Item 15 from file: 442)
DIALOG(R)File 442:AMA Journals

00051130

The **AIDS** litigation project: a national review of court and human rights commission decisions, part I: the social impact of **AIDS**. (acquired immunodeficiency syndrome)

Gostin, Lawrence O.
JAMA, The Journal of the American Medical Association
April 11, 1990; v263: p1961(10)
LINE COUNT: 01019

Infection with human immunodeficiency virus (**HIV**) has led to the largest body of legal cases regarding a disease in United States history. A review is provided of 469 cases and is the first of a two-part series. Education about **AIDS** (acquired immune deficiency syndrome, the disease with which **HIV** is associated) has been challenged as potentially offensive, especially in schools. Litigation is directed against hospitals that did not screen blood for **HIV** or recommend that donors with high-risk behavior refrain from giving blood. Reporting of people with **HIV** , especially relevant now that azidothymidine (AZT, also known as zidovudine, the only approved drug for treating **AIDS**)

exists, is required by only 28 states, and physician groups have sued to increase reporting. Anonymous testing has brought litigation, as have attempts to screen prospective foreign visitors to prevent their entering the country. Several cases have been brought against **HIV**-positive people who bit or spit at others, or who infected others through sexual contact. It is difficult to determine, however, if a person intended to transmit the disease, even if he entered a sexual relationship knowing he was seropositive (tested positive). After rape, however, the right of the victim to know is increasingly being upheld, but the accused also has the right to not be tested before a trial has even begun. Public gathering places such as bath-houses and adult video shops and bookstores have been closed, but First Amendment rights may have been abridged in some cases, especially regarding the sale of books or movies. 'Dial-a-porn' has been upheld so long as the messages are not obscene, only indecent. Lawsuits have been filed against companies selling **AIDS**-related drugs, and the home test kit for **HIV** antibody has not been approved because of the importance of proper diagnosis and counselling. Telling a judge or jurors that a person has **AIDS** when it is irrelevant to a case has brought lawsuits. Lawsuits been filed by people with **AIDS** who blame a hospital, physician, or lover. **AIDS** patients need to make important decisions about treatment and their estates, and these become complicated legal issues when the disease itself can cause dementia. Family law has been affected by **AIDS** , and a spouse who knows he has a sexually transmitted infection, lies to his spouse, and transmits the infection, can be held liable. In general, courts have not found that **HIV** infection is relevant to determining a child's best interests. Rights of patients to confidentiality are in obvious conflict with the right of others to know they may be exposed to infection, and cases have been brought from both sides. Public health concerns, however, can take

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The epidemiology of tuberculosis among North Carolina migrant farm workers.

Ciesielski, Stephen D.; Seed, John R.; Esposito, Douglas H.; Hunter, Nancy
JAMA, The Journal of the American Medical Association
April 3, 1991; v265: p1715(5)
LINE COUNT: 00416

Tuberculosis (TB) is a disease caused by infection with the bacteria Mycobacterium tuberculosis. It is characterized by inflammation, formation of tubercles (node-like lesions), tissue death, formation of fiber-like tissue, and deposition of calcium. The disease commonly affects the respiratory system but may also involve other organ systems. The incidence of TB decreased until the mid-1980s, when the prevalence of TB increased again in association with human immunodeficiency virus (**HIV**) infection. TB occurs with increased frequency among minorities, the homeless, prisoners, alcoholics, and the poor. Farm workers often originate from Mexico, Central America, and Haiti, where TB occurs with much greater frequency than in the United States. The epidemiology of TB among farm workers must be assessed in order to decrease the overall incidence of this disease. In 1988, the epidemiology of TB among migrants was assessed in 543 farm workers in North Carolina. Immunological evidence of TB was obtained in 33 percent of Hispanics, 54 percent of blacks born in the United States, and 76 percent of Haitians. Active TB was identified in 3.6 percent of American blacks and 0.5 percent of Hispanics. These findings suggest that TB is a serious health problem among farm workers, and that it may be

addressed by providing additional resources for migrant health care, improving their access to health care, and reducing the transmission of TB. (Consumer Summary produced by Reliance Medical Information, Inc.)

4/3,AB/18 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00120284

A Comparison of Nefazodone, the Cognitive Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of Chronic Depression (Original Articles)

Keller, Martin B.; McCullough, James P.; Klein, Daniel N.; Arnow, Bruce; Dunner, David L.; Gelenberg, Alan J.; Markowitz, John C.; Nemeroff, Charles B.; Russell, James M.; Thase, Michael E.; Trivedi, Madhukar H.; Zajecka, John; Blalock, Janice A.; Borian, Francis E.; DeBattista, Charles; Fawcett, Jan; Hirschfeld, Robert M.A.; Jody, Darlene N.; Keitner, Gabor; Kocsis, James H.; Koran, Lorrin M.; Kornstein, Susan G.; Manber, Rachel; Miller, Ivan; Ninan, Philip T.; Rothbaum, Barbara; Rush, A. John; Schatzberg, Alan F.; Vivian, Dina.
The New England Journal of Medicine
May 18, 2000; 342 (20),pp 1462-1470
LINE COUNT: 00401 WORD COUNT: 05547

Abstract

Background: Patients with chronic forms of major depression are difficult to treat, and the relative efficacy of medications and psychotherapy is uncertain.

Methods: We randomly assigned 681 adults with a chronic nonpsychotic major depressive disorder to 12 weeks of outpatient treatment with nefazodone (maximal dose, 600 mg per day), the cognitive behavioral-analysis system of psychotherapy (16 to 20 sessions), or both. At base line, all patients had scores of at least 20 on the 24-item Hamilton Rating Scale for Depression (indicating clinically significant depression). Remission was defined as a score of 8 or less at weeks 10 and 12. For patients who did not have remission, a satisfactory response was defined as a reduction in the score by at least 50 percent from base line and a score of 15 or less. Raters were unaware of the patients' treatment assignments.

Results: Of the 681 patients, 662 attended at least one treatment session and were included in the analysis of response. The overall rate of response (both remission and satisfactory response) was 48 percent in both the nefazodone group and the psychotherapy group, as compared with 73 percent in the combined-treatment group ($P<0.001$ for both comparisons). Among the 519 subjects who completed the study, the rates of response were 55 percent in the nefazodone group and 52 percent in the psychotherapy group, as compared with 85 percent in the combined-treatment group ($P<0.001$ for both comparisons). The rates of withdrawal were similar in the three groups. Adverse events in the nefazodone group were consistent with the known side effects of the drug (e.g., headache, somnolence, dry mouth, nausea, and dizziness).

Conclusions: Although about half of patients with chronic forms of major depression have a response to short-term treatment with either nefazodone or a cognitive behavioral-analysis system of psychotherapy, the combination of the two is significantly more efficacious than either treatment alone. (N Engl J Med 2000;342:1462-70.)

4/3,AB/19 (Item 2 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00119848

Mechanisms of Disease: Inflammatory Skin Diseases, T Cells, and Immune Surveillance (Review Articles)

Robert, Caroline; Kupper, Thomas S.
The New England Journal of Medicine
Dec 9, 1999; 341 (24),pp 1817-1828
LINE COUNT: 00662 WORD COUNT: 09145

4/3,AB/20 (Item 3 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00111836

Medical Progress: Progress In Psychiatry (Second of Two Parts) (Review Articles)

Michels, Robert; Marzuk, Peter M.
The New England Journal of Medicine
Aug 26, 1993; 329 (9),pp 628-638
LINE COUNT: 00799 WORD COUNT: 11032

4/3,AB/21 (Item 4 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00111268

The Threat Of Infectious Diseases In Somalia (Special Reports)

Heppner, D. Gray Jr.; Magill, Alan J.; Gasser, Robert A. Jr.; Oster, Charles N.
The New England Journal of Medicine
Apr 8, 1993; 328 (14),pp 1061-1068
LINE COUNT: 00456 WORD COUNT: 06295

4/3,AB/22 (Item 5 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00109586

Medical Progress: Recent Advances In Dermatology (Review Article)

Phillips, Tania J.; Dover, Jeffrey S.
The New England Journal of Medicine
Jan 16, 1992; 326 (3),pp 167-178
LINE COUNT: 00668 WORD COUNT: 09227

4/3,AB/23 (Item 6 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

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Medical Progress: Bacterial And Protozoal Gastroenteritis (Review Article)

Guerrant, Richard L.; Bobak, David A.
The New England Journal of Medicine
Aug 1, 1991; 325 (5),pp 327-340
LINE COUNT: 00741 WORD COUNT: 10238

4/3,AB/24 (Item 7 from file: 444)
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00108498
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Medical Aspects Of The Persion Gulf War: The Threat Of Infectious Disease In Americans Returning From Operation Desert Storm (Special Reports)

Gasser, Robert A.; Magill, Alan J.; Oster, Charles N.; Tramont, Edmund C.
The New England Journal of Medicine
Mar 21, 1991; 324 (12),pp 859-864
LINE COUNT: 00319 WORD COUNT: 04412

4/3,AB/25 (Item 8 from file: 444)
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Weekly Clinicopathological Exercises: Case 15-1990: A 78-Year-Old Woman From The Dominican Republic With Chronic Diarrhea (Case Records of the Massachusetts General Hospital)

Trier, Jerry S.; Donnelly, Susan M.
The New England Journal of Medicine
Apr 12, 1990; 322 (15),pp 1067-1075
LINE COUNT: 00655 WORD COUNT: 09042

4/3,AB/26 (Item 9 from file: 444)
DIALOG(R)File 444:New England Journal of Med.
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00106303
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Ethanol And The Nervous System (Medical Progress)

Charness, Michael E.; Simon, Roger P.; Greenberg, David A.
The New England Journal of Medicine
Aug 17, 1989; 321 (7),pp 442-454
LINE COUNT: 00878 WORD COUNT: 12129